STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 135899

TO: Deborah Lambkin
Location:
Art Unit: 1626
October 23, 2004

Case Serial Number: 10/830125

From: P. Sheppard
Location: Remsen Building
Phone: (571) 272-2529

sheppard@uspto.gov

Search Notes

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FILE COVERS 1907 - 23 Oct 2004  VOL 141 ISS 18
FILE LAST UPDATED: 22 Oct 2004  (20041022/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


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L8   ANSWER 1 OF 6  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2004:60147  HCAPLUS
DOCUMENT NUMBER:          140:111291
TITLE:                    Preparation of substituted 5-aryl-benzothiepines as
                          ileal bile acid transport and taurocholate uptake
                          inhibitors
INVENTOR(S):              Lee, Len F.; Banerjee, Shyamal C.; Huang, Horng Chih;
                          Li, Jinglin J.; Miller, Raymond E.; Reitz, David B.;
                          Tremont, Sanuel J.
PATENT ASSIGNEE(S):       G.D. Searle and Co., USA
SOURCE:                   U.S. Pat. Appl. Publ., 235 pp., Cont.-in-part of U.S.
                          Ser. No. 831,284.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   9
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.          DATE
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     US 2004014803        A1    20040122    US 2002-68297            20020208
     US 6784201           B2    20040831
     EP 1440972           A1    20040728    EP 2004-10088            19970311
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI
     AU 761249            B2    20030529    AU 2000-53394            20000816
     US 2002013476        A1    20020131    US 2001-828968           20010409
     US 6387924           B2    20020514
     US 2003171426        A1    20030911    US 2002-76091            20020215
     US 6642268           B2    20031104
     US 2004204478        A1    20041014    US 2004-830125           20040423
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                                             US 1997-816065      A2 19970311
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US	2001-828968	A3 20010409
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EP	1997-915976	A3 19970311
US	1997-40660P	P 19970311
US	1997-68170P	P 19971219
US	1998-109551	A2 19980702
US	1999-275463	A1 19990324
US	1999-443403	A1 19991119
US	2000-676466	A3 20000929
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OTHER SOURCE(S): MARPAT 140:111291

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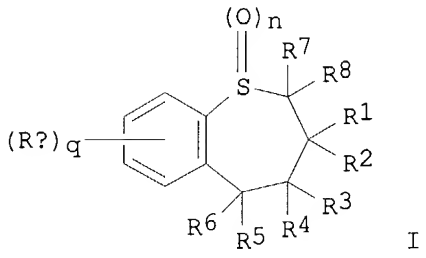

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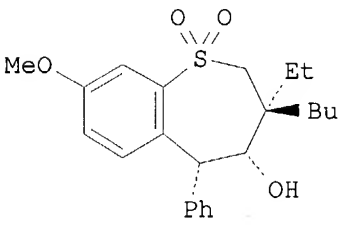

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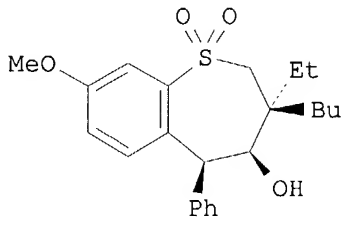

III

AB The title compds. (I) [wherein q = 1-4; n = 0-2; R1, R2 = H, (un)substituted (halo)alkyl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy(alkyl), dialkylamino, alkylthio, (polyalkyl)aryl, or cycloalkyl; or R1 and R2 taken together with the atoms to which they are attached = cycloalkyl; R3, R4 = H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocyclyl, OR9, NR9R10, SR9, S(O)R9, SO2R9, or SO3R9; R9, R10 = H, (cyclo)alkyl, alkenyl, alkynyl, aryl(alkyl), acyl, heterocyclyl, or ammoniumalkyl; or R3 and R4 together = :O, :NOR11, :S, :NNR11R12, :NR9, or :CR11R12; R11, R12 = H, (cyclo)alkyl, alkenyl, alkynyl, aryl(alkyl), heterocyclyl, carboxylalkyl, carboalkoxyalkyl, cyanoalkyl, OR9, NR9R10, SR9, S(O)R9, SO2R9, SO3R9, CO2R9, CN, halo, oxo, or CONR9R10; R5, R6 = H, alkyl, aryl, etc.; R7, R8 = H, alkyl; Rx = H, (un)substituted (cyclo)alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl(alkyl), halo(alkyl), (quaternary) heterocyclyl, (quaternary) heteroaryl, polyether, alkoxy, amino, alkylthio, NO2, carboxy, carbamido, etc.] were prepared for the prophylaxis and treatment of hyperlipidemic conditions, such as those associated with atherosclerosis or hypercholesterolemia. Thus, KOBu-t was added to a solution of 2-((2-benzyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (preparation given) and dry THF cooled to -1.6°C to give, after workup, II and III (96% combined yield). The isomers were separated upon recrystn. II inhibited IBAT-mediated uptake of [14C]-taurocholate in H14 cells with an IC50 of 0.1 μM and reduced serum cholesterol from 143 mg (7%) to 126 mg (2%) compared to control in cholesterol-fed hamsters in a 14-day test. In vitro taurocholate uptake assay data are included for nearly 600 compds. of the invention.

IT **197373-18-5P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

L8 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:376848 HCAPLUS
DOCUMENT NUMBER: 138:385315
TITLE: Mono- and di-fluorinated benzothiepines as inhibitors of apical sodium co-dependent bile acid transport (ASBT) and taurocholate uptake for treating hyperlipidemic conditions and methods for preparation
INVENTOR(S): Koeller, Kevin J.; Tremont, Samuel J.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: PCT Int. Appl., 589 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003040127	A1	20030515	WO 2002-US35257	20021104
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004067872	A1	20040408	US 2002-286987	20021104
US 6740663	B2	20040525		
EP 1448546	A1	20040825	EP 2002-778711	20021104
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 2004176438	A1	20040909	US 2003-743404	20031223
PRIORITY APPLN. INFO.:			US 2001-330892P	P 20011102
			US 2002-286987	A3 20021104
			WO 2002-US35257	W 20021104

OTHER SOURCE(S): MARPAT 138:385315
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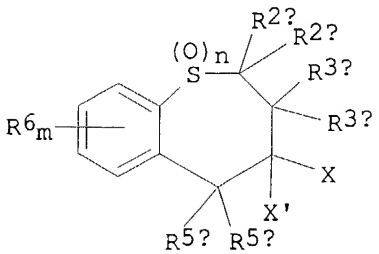

I

AB Mono-fluorinated and di-fluorinated benzothiepine apical Na co-dependent bile acid transport (ASBT) inhibitors (shown as I; variables defined below; no specific examples are included) are disclosed together with methods of making the same, methods of using the same to treat hyperlipidemic conditions as well as pharmaceutical compns. containing the same compds. For I: X = F, X' = H, F; n = 0-2; m = 0-4; R2A and R2B = H and hydrocarbyl; R3A, R3B, R5A, and R5B = H, alkyl, cycloalkyl, alkenyl, alkynyl, heterocyclyl, quaternary heterocyclyl, oxo, aryl-R5, -OR9, -NR9R10, -SR9, -S(O)R9, -SO2R9, and -SO3R9; R9 and R10 = H, hydrocarbyl, amino, and hydrocarbylamino. R5 = H, hydrocarbyl, heterocyclyl, quaternary heterocyclyl, -OR9, -SR9, -S(O)R9, -SO2R9, and -SO3R9; ≥1 R6 radicals = H, halogen, -CN, -NO2, hydrocarbyl, -R5, -OR13, -NR 13R14, -SR13, -S(O)R13, -S(O)2R13, -SO3R13, -S+R3R14A-, -NR13OR14, -NR13NR14R15, -OM, -SO2OM, -SO2NR13R14, -NR14C(O)R13, -C(O)OM, -S(O)NR13R14, -N+R13R14R15A-, -PR13R14, -P(O)R13R4, -P+R13R14R15A-, amino acid residue, peptide residue, polypeptide residue, and carbohydrate residue; addnl. details are given in the claims. I (X = X' = F) are claimed to be preparable from the 4-oxo analog and diethylaminosulfur trifluoride; I (X = F; X' = H) are claimed preparable from the 4-hydroxy analog and diethylaminosulfur trifluoride. Hundreds of example prepns. of precursors to I are included, but none of I; most of the example prepns. have appeared in earlier patents (e.g. WO 98/40375). Biol. testing procedures are described but no test results are reported except for the statement that a polyethylene glycol-functionalized benzothiepine (4500 MW; a 4-hydroxy analog of I) inhibited ileal bile acid transport-mediated uptake of 14C-taurocholate in H14 cells.

IT **197373-18-5P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of precursors of mono- and di-fluorinated benzothiepine inhibitors of apical sodium co-dependent bile acid transport (ASBT) and taurocholate uptake for treating hyperlipidemic conditions)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:560070 HCAPLUS
DOCUMENT NUMBER: 135:137410
TITLE: Preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors.
INVENTOR(S): Keller, Bradley T.; Glenn, Kevin C.; Manning, Robert E.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: U.S., 356 pp., Cont.-in-part of U.S. Ser. No. 831,284, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6268392	B1	20010731	US 1998-37308	19980309
EP 1440972	A1	20040728	EP 2004-10088	19970311
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
AU 761249	B2	20030529	AU 2000-53394	20000816
US 6420417	B1	20020716	US 2000-676466	20000929
US 2003171426	A1	20030911	US 2002-76091	20020215
US 6642268	B2	20031104		
US 2004157915	A1	20040812	US 2003-620460	20030717
PRIORITY APPLN. INFO.:			US 1994-305526 A2	19940912

US	1995-517051	A1 19950821
US	1996-13119P	P 19960311
US	1997-40660P	P 19970311
US	1997-816065	A2 19970311
US	1997-831284	B2 19970331
AU	1997-23266	A3 19970311
EP	1997-915976	A3 19970311
US	1998-37308	A3 19980309
US	2000-676466	A3 20000929
US	2002-76091	A1 20020215

OTHER SOURCE(S): MARPAT 135:137410
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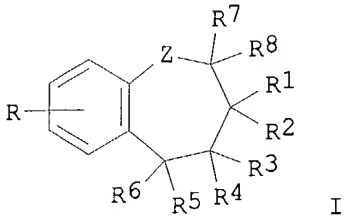

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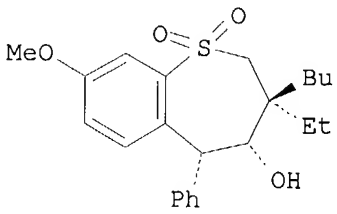

II

AB Title compds. [I; R = H or 1-4 of alkyl, alkenyl, alkynyl, acyloxy, aryl, aralkyl, halo, etc.; R1, R2 = H, (substituted) alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, alkoxy, dialkylamino, etc.; R1R2C = cycloalkylidene; R3, R4 = H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocyclyl, heteroaryl, etc.; R3R4 = O, S, NOR11, etc.; R11 = H, alkyl, alkenyl, alkynyl, aryl, aralkyl, etc.; R5, R6 = H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl, etc.; R7, R8 = H, alkyl; Z = SO0-2], were prepared A composition comprising an ileal bile acid transport inhibitor and an HMG Co-A reductase inhibitor is claimed. Thus, title compound (II) (preparation via 2-mercapto-4-methoxybenzophenone given) at 0.2% as an ileal perfusion in guinea pigs reduced HDL cholesterol from 89 mg% to 76 mg%.

IT **197373-18-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:590035 HCAPLUS
DOCUMENT NUMBER: 133:193089
TITLE: Preparation of substituted 5-aryl-benzothiepines as ileal bile acid transport and taurocholate uptake inhibitors
INVENTOR(S): Lee, Len F.; Banerjee, Shyamal C.; Huang, Horng-chih; Li, Jinglin J.; Miller, Raymond E.; Reitz, David B.; Tremont, Samuel J.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: U.S., 191 pp., Cont.-in-part of U. S. Ser. No. 109,551.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6107494	A	20000822	US 1999-275463	19990324
EP 1440972	A1	20040728	EP 2004-10088	19970311
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US 5994391	A	19991130	US 1998-109551	19980702
EP 1331225	A1	20030730	EP 2003-5459	19981216
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CA 2336315	AA	20000113	CA 1999-2336315	19990629
WO 2000001687	A1	20000113	WO 1999-US12828	19990629
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RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9948202	A1	20000124	AU 1999-48202	19990629
AU 766957	B2	20031030		
EP 1091953	A1	20010418	EP 1999-931769	19990629
EP 1091953	B1	20031210		
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TR 200100824	T2	20010723	TR 2001-200100824	19990629
BR 9911737	A	20011211	BR 1999-11737	19990629
EE 200100002	A	20020617	EE 2001-2	19990629
JP 2002519418	T2	20020702	JP 2000-558091	19990629
NZ 509621	A	20030829	NZ 1999-509621	19990629
AT 256122	E	20031215	AT 1999-931769	19990629
PT 1091953	T	20040430	PT 1999-931769	19990629
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AU 761249	B2	20030529	AU 2000-53394	20000816
NO 2001000016	A	20010302	NO 2001-16	20010102
ZA 2001000028	A	20010725	ZA 2001-28	20010102
HR 2001000004	A1	20011231	HR 2001-4	20010102
BG 105206	A	20010928	BG 2001-105206	20010131
US 2002013476	A1	20020131	US 2001-828968	20010409
US 6387924	B2	20020514		
US 2002188119	A1	20021212	US 2002-72600	20020211
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US 6642268	B2	20031104		
JP 2004203891	A2	20040722	JP 2004-50473	20040225
US 2004204478	A1	20041014	US 2004-830125	20040423

PRIORITY APPLN. INFO.:

US 1994-305526	B2	19940913
US 1995-517051	B1	19950821
US 1996-13119P	P	19960311
US 1997-816065	B2	19970311
US 1997-831284	B2	19970331
US 1997-68170P	P	19971219
US 1998-109551	A2	19980702
AU 1997-23266	A3	19970311
EP 1997-915976	A3	19970311
US 1997-40660P	P	19970311
EP 1998-962044	A3	19981216
US 1999-275463	A1	19990324
EP 1999-931769	A3	19990629
JP 2000-558091	A3	19990629
WO 1999-US12828	W	19990629

US 1999-443403 A1 19991119
US 2000-676466 A3 20000929
US 2000-581897 A3 20001002
US 2001-828968 A3 20010409
US 2002-68297 A3 20020208

OTHER SOURCE(S): MARPAT 133:193089

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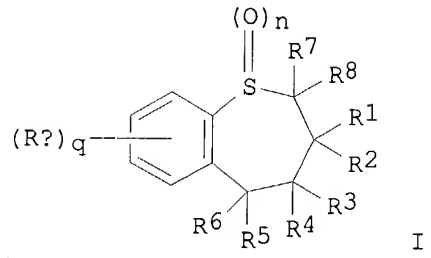

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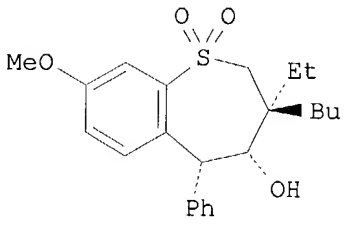

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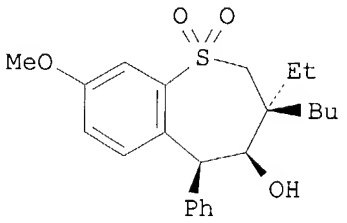

III

AB The title compds. (I) [wherein q = 1-4; n = 2; R1 and R2 = independently H or (un)substituted (halo)alkyl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy(alkyl), dialkylamino, alkylthio, (polyalkyl)aryl, or cycloalkyl; or R1 and R2 taken together with the atoms to which they are attached = cycloalkyl; R3 and R4 = independently H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocyclyl, OR9, NR9R10, SR9, S(O)R9, SO2R9, or SO3R9; R9 and R10 = independently H, (cyclo)alkyl, alkenyl, alkynyl, aryl(alkyl), acyl, heterocyclyl, or ammoniumalkyl; or R3 and R4 together = :O, :NOR11, :S, :NNR11R12, :NR9, or :CR11R12; R11 and R12 = independently H, (cyclo)alkyl, alkenyl, alkynyl, aryl(alkyl), heterocyclyl, carboxylalkyl, carboalkoxyalkyl, cyanoalkyl, OR9, NR9R10, SR9, S(O)R9, SO2R9, SO3R9, CO2R9, CN, halo, oxo, or CONR9R10; R5 = substituted aryl; R6 = H; R7 and R8 = independently H or alkyl; Rx = independently H or (un)substituted (cyclo)alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl(alkyl), halo(alkyl), (quaternary) heterocyclyl, (quaternary) heteroaryl, polyether, alkoxy, amino, alkylthio, NO2, carboxy, carbamido, etc.] where prepared for the prophylaxis and treatment of hyperlipidemic conditions, such as those associated with atherosclerosis or hypercholesterolemia. Thus, KOBu-t was added to a solution of 2-((2-benzyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (preparation given) and dry THF cooled to -1.6°C to give, after workup, II and III (96% combined yield). The isomers were separated upon recrystn. II inhibited IBAT-mediated uptake of [14C]-taurocholate in H14 cells with an IC50 of 0.1 μM and reduced serum cholesterol from 143 mg (7%) to 126 mg (2%) compared to control in cholesterol-fed hamsters in a 14-day test. In vitro taurocholate uptake assay data are included for nearly 600 compds. of the invention.

IT **197373-18-5P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as

ileal bile acid transport and taurocholate uptake inhibitors)
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:621210 HCAPLUS
DOCUMENT NUMBER: 129:260353
TITLE: Preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors.
INVENTOR(S): Reitz, David B.; Lee, Len F.; Li, Jinglin J.; Huang, Horng-Chih; Tremont, Samuel J.; Miller, Raymond E.; Baneriee, Shyamal C.; Manning, Robert E.; Glenn, Kevin C.; Keller, Bradley T.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA; et al.
SOURCE: PCT Int. Appl., 477 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9840375	A2	19980917	WO 1998-US3792	19980310
WO 9840375	A3	19981203		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9864408	A1	19980929	AU 1998-64408	19980310
AU 730024	B2	20010222		
EP 971744	A2	20000119	EP 1998-910075	19980310
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NZ 337830	A	20010727	NZ 1998-337830	19980310
BR 9808013	A	20010925	BR 1998-8013	19980310
JP 2002500628	T2	20020108	JP 1998-539594	19980310
NO 9904390	A	19991104	NO 1999-4390	19990910
AU 761249	B2	20030529	AU 2000-53394	20000816
US 2003171426	A1	20030911	US 2002-76091	20020215
US 6642268	B2	20031104		

PRIORITY APPLN. INFO.:

US 1997-40660P	P	19970311
US 1994-305526	B2	19940913
US 1995-517051	B1	19950821
US 1996-13119P	P	19960311
AU 1997-23266	A3	19970311
US 1997-816065	B2	19970311
US 1997-831284	B3	19970331
WO 1998-US3792	W	19980310
US 2000-676466	A3	20000929

OTHER SOURCE(S): MARPAT 129:260353
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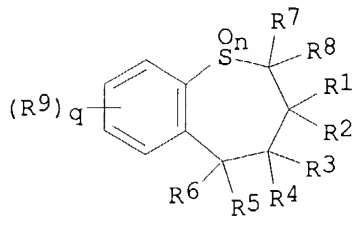

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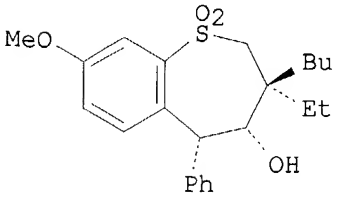

II

AB Title compds. [I; q = 1-4; n = 0-2; R1, R2 = H, (substituted) alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, alkoxy, dialkylamino, etc.; R1R2C = cycloalkylidene; R3, R4 = H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocyclyl, heteroaryl, etc.; R3R4 = O, S, NOR11, etc.; R11 = H, alkyl, alkenyl, alkynyl, aryl, aralkyl, etc.; R5, R6 = H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl, etc.; R7, R8 = H, alkyl; R9 = H, alkyl, alkenyl, alkynyl, acyloxy, aryl, aralkyl, halo, etc.], were prepared A composition comprising an ileal bile acid transport inhibitor and an HMG Co-A reductase inhibitor is claimed. Thus, title compound (II) (preparation via 2-mercapto-4-methoxybenzophenone given) at 0.2% as an ileal perfusion in guinea pigs reduced HDL cholesterol from 89 mg% to 76 mg%.

IT **197373-18-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

L8 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:623163 HCAPLUS
DOCUMENT NUMBER: 127:307312
TITLE: Novel benzothiepines having activity as inhibitors of ileal bile acid transport and taurocholate uptake
INVENTOR(S): Reitz, David B.; Lee, Len F.; Li, Jinglin J.; Huang, Horng-Chih; Tremont, Samuel J.; Miller, Raymond E.; Banerjee, Shyamal C.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA; Reitz, David B.; Lee, Len F.; Li, Jinglin J.; Huang, Horng-Chih; Tremont, Samuel J.; Miller, Raymond E.; Banerjee, Shyamal C.
SOURCE: PCT Int. Appl., 406 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9733882	A1	19970918	WO 1997-US4076	19970311
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2248586	AA	19970918	CA 1997-2248586	19970311
AU 9723266	A1	19971001	AU 1997-23266	19970311
AU 723123	B2	20000817		
EP 888333	A1	19990107	EP 1997-915976	19970311

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
CN 1221414	A	19990630	CN 1997-194503	19970311
CN 1110494	B	20030604		
BR 9708042	A	19990727	BR 1997-8042	19970311
JP 2001526627	T2	20011218	JP 1997-532875	19970311
RU 2202549	C2	20030420	RU 1998-118643	19970311
EP 1440972	A1	20040728	EP 2004-10088	19970311
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
NO 9804146	A	19981030	NO 1998-4146	19980909
AU 761249	B2	20030529	AU 2000-53394	20000816
US 2003171426	A1	20030911	US 2002-76091	20020215
US 6642268	B2	20031104		
PRIORITY APPLN. INFO.:			US 1996-13119P	P 19960311
			US 1997-816065	A 19970311
			US 1994-305526	B2 19940913
			US 1995-517051	B1 19950821
			AU 1997-23266	A3 19970311
			EP 1997-915976	A3 19970311
			US 1997-40660P	P 19970311
			WO 1997-US4076	W 19970311
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			US 2000-676466	A3 20000929

OTHER SOURCE(S): MARPAT 127:307312

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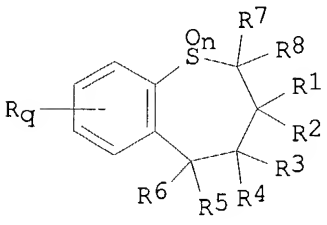

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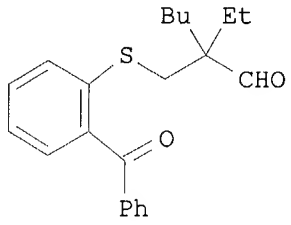

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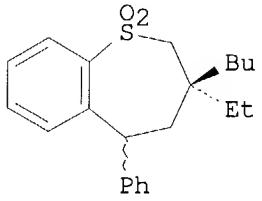

III

AB Novel benzothiepines I [q = 1-4; n = 0-2; R = H, halo, (un)substituted alk(en/yn)yl, acyloxy, aryl, heterocyclyl, OH or NH2 or SH or derivs., etc.; R1, R2 = H, (un)substituted and/or heteroatom-replaced alk(en/yn)yl, cycloalkyl, aryl, alkoxy, alkylthio, dialkylamino; or CR1R2 = C3-10 cycloalkylidene; R3, R4 = H, alk(en/yn)yl, acyloxy, aryl, heterocyclyl, OH or NH2 or SH or derivs.; or R3R4 = O, S, NH, NOH, NNH2, CH2 or derivs.; R5, R6 = H, (un)substituted alk(en/yn)yl, cycloalkyl, aryl, heterocyclyl, OH or SH or derivs.; R7, R8 = H, alkyl] and their derivs. and analogs are provided. Also provided are pharmaceutical compns. containing I and methods of their medical use, particularly in the prophylaxis and treatment of hyperlipidemic conditions, such as those associated with atherosclerosis or hypercholesterolemia. For instance, the keto aldehyde II was cyclized by Zn/TiCl3, and the resultant cycloolefin was oxidized and epoxidized by m-ClC6H4C(O)OOH and hydrogenated over Pd/C to give epimeric title compds.

α- and β-III in 25% and 13% yield, plus addnl. compds. In a test for inhibition of IBAT-mediated uptake of [14C]-taurocholate in H14 cells in vitro, β-III had an IC50 of 5 μM.

IT **197373-18-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzothiepines as antihyperlipidemics)

=> => fil reg
FILE 'REGISTRY' ENTERED AT 13:44:42 ON 23 OCT 2004
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STRUCTURE FILE UPDATES: 21 OCT 2004 HIGHEST RN 767117-28-2
DICTIONARY FILE UPDATES: 21 OCT 2004 HIGHEST RN 767117-28-2

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

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Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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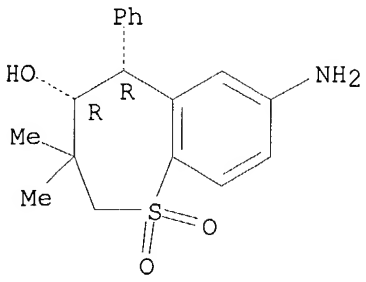
L7 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 197373-18-5 REGISTRY
CN 1-Benzothiepin-4-ol, 7-amino-2,3,4,5-tetrahydro-3,3-dimethyl-5-phenyl-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Benzothiepin-4-ol, 7-amino-2,3,4,5-tetrahydro-3,3-dimethyl-5-phenyl-, 1,1-dioxide, cis-
FS STEREOSEARCH
MF C18 H21 N O3 S
SR CA
LC STN Files: CA, CAPLUS, USPAT2, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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6 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:111291

REFERENCE 2: 138:385315

REFERENCE 3: 135:137410

REFERENCE 4: 133:193089

REFERENCE 5: 129:260353

REFERENCE 6: 127:307312

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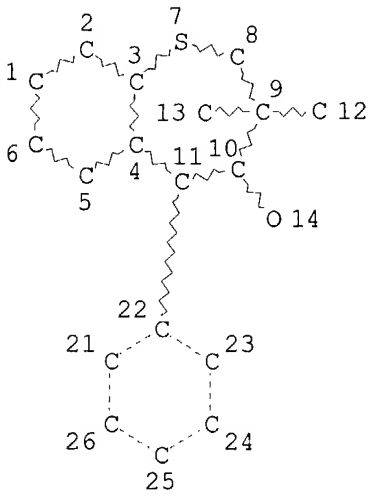

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
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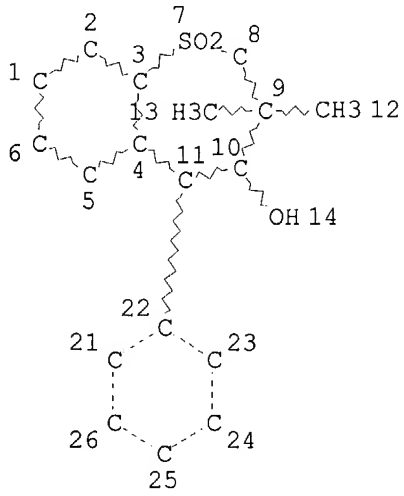
L6 STR



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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
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L8 6 SEA FILE=HCAPLUS ABB=ON PLU=ON L7
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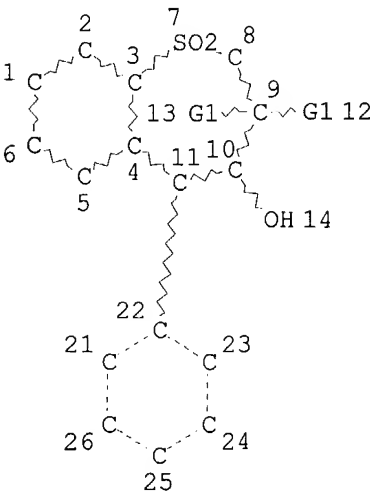

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DEFAULT MLEVEL IS ATOM
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GRAPH ATTRIBUTES:

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NUMBER OF NODES IS  20

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L16       28099 SEA FILE=HCAPLUS ABB=ON  PLU=ON  LI J?/AU,IN
L17       72622 SEA FILE=HCAPLUS ABB=ON  PLU=ON  MILLER?/AU,IN
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                OR L16 OR L17 OR L18 OR L19))

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L20  ANSWER 1 OF 20  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2004:740309  HCAPLUS
DOCUMENT NUMBER:          141:260784
TITLE:                    Preparation of benzothiazepine and benzothiepine
                          derivatives as ileal bile acid transport (IBAT)
                          inhibitors
INVENTOR(S):              Starke, Ingemar; Alenfalk, Suzanne; Nordberg, Mats
                          Peter; Dahlstrom, Mikael Ulf Johan; Bostrom, Stig
                          Jonas; Lemurell, Malin Anita; Wallberg, Andreas
                          Christer
PATENT ASSIGNEE(S):       Astrazeneca Ab, Swed.; Astrazeneca Uk Limited
SOURCE:                   PCT Int. Appl., 77 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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     WO 2004076430         A1    20040910    WO 2004-GB695           20040223
         W:  AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG,
             BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR,
             CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES,
             ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN,
             IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC,
             LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX,
             MZ, MZ, NA, NI
         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
             BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
             MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
             GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN,
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PRIORITY APPLN. INFO.:                       GB 2003-4194        A  20030225
GI
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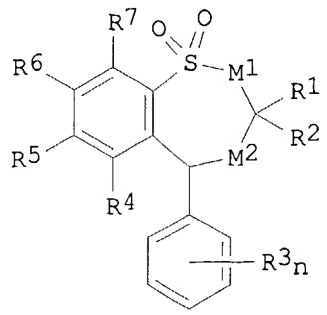

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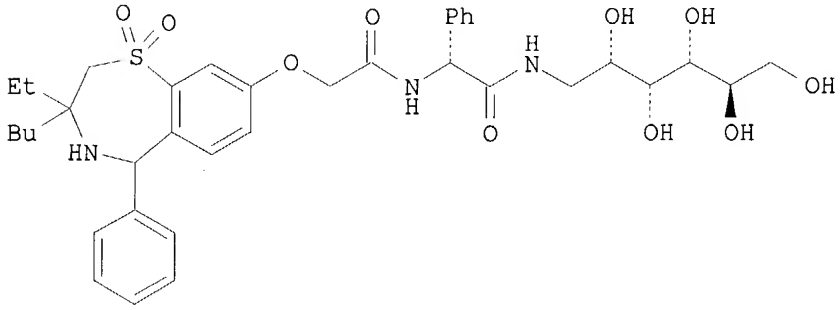


II

AB Title compds. represented by the formula I [wherein R1, R2 = H, alkyl, alkenyl; R3 = halo, nitro, cyano, amino, etc.; R5, R6 = independently H, hydroxy, (un)substituted carbamoylalkyloxy, etc.; R4, R7 = independently H, halo, mercapto, alkenyl, etc.; M1, M2 = independently (un)substituted carbon or amino; n = 0-5; and pharmaceutically acceptable salts, solvates, solvates of such a salt or a prodrug thereof] were prepared as ileal bile acid transport (IBAT) inhibitors. For example, reaction of (±)-trans-1,1-Dioxo-3-ethyl-3-butyl-5-phenyl-8-(carboxymethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine with (R)-4-[N'-[2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl]carbamoyl]benzylamine gave II. Thus, I and their pharmaceutical compns. are useful as ileal bile acid transport (IBAT) inhibitors for the treatment of hyperlipidemia (no data).

IT **753486-44-1P 753486-46-3P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzothiazepine and benzothiepine derivs. as ileal bile acid transport (IBAT) inhibitors)

IT **501923-61-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of benzothiazepine and benzothiepine derivs. as ileal bile acid transport (IBAT) inhibitors)

IT **501923-58-6P 501923-60-0P 753010-63-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of benzothiazepine and benzothiepine derivs. as ileal bile acid transport (IBAT) inhibitors)

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 2 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:523671 HCAPLUS
DOCUMENT NUMBER: 141:133877
TITLE: Inhibition of ileal bile acid transport lowers plasma cholesterol levels by inactivating hepatic farnesoid X

receptor and stimulating cholesterol 7α-hydroxylase

AUTHOR(S): Li, Hai; Xu, Guorong; Shang, Quan; Pan, Luxing; Shefer, Sarah; Batta, Ashok K.; Bollineni, Jaya; Tint, G. Stephen; Keller, Brad T.; Salen, Gerald

CORPORATE SOURCE: Department of Medicine, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA

SOURCE: Metabolism, Clinical and Experimental (2004), 53(7), 927-932
CODEN: METAAJ; ISSN: 0026-0495

PUBLISHER: Elsevier Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We investigated the effect of SC-435, a competitive inhibitor of ileal apical sodium-dependent bile acid cotransporter (ASBT) on ileal bile acid absorption and the hepatic nuclear receptor FXR (farnesoid X receptor), which regulates cholesterol 7α-hydroxylase (CYP7A1) activity and mRNA levels. Eighteen New Zealand White (NZW) rabbits were divided into 2 groups: controls (n = 10) and fed SC-435 125 mg/kg/d for 1 wk (n = 8). In rabbits treated with SC-435, fecal bile acid outputs increased by more than 8 times, reflecting substantial bile acid malabsorption. Plasma cholesterol levels decreased 26%, while bile acid pool sizes and biliary bile acid outputs did not change after treatment. CYP7A1 activity increased 64% and mRNA rose by 4 times after treatment. The expression of FXR target genes in the liver, short heterodimer partner (SHP) and bile salt export pump (BSEP), decreased 11.6 and 2.6 times, resp., after treatment, which indicates inactivation of hepatic FXR. However, the mRNA levels of ileal bile acid binding protein (IBABP) did not change significantly, while ileal ASBT mRNA expression increased by 2.4 times after treatment. Rabbits treated with SC-435 developed ileal bile acid malabsorption, which decreased the return of bile acids (FXR ligands) to the liver to inactivate hepatic FXR, which upregulated CYP7A1 and lowered plasma cholesterol levels. Although fecal bile acid malabsorption was substantial, increased bile acid production from hepatic cholesterol kept biliary bile acid outputs intact. Thus, a new balance was reached in the liver, where increased bile acid synthesis compensated for diminished ileal bile acid absorption to maintain the circulating enterohepatic bile acid pool.

IT **289037-67-8**, SC-435
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ASBT inhibitor SC-435 lowers cholesterol by effect on ileal bile acid transport, hepatic FXR, and cholesterol 7α-hydroxylase)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 3 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:492306 HCAPLUS

DOCUMENT NUMBER: 141:17641

TITLE: Methods and compositions for the prevention and treatment of Alzheimer's disease with intestinal bile acid reuptake inhibitors

PATENT ASSIGNEE(S): Aventis Pharma SA, Fr.

SOURCE: Fr. Demande, 25 pp.
CODEN: FRXXBL

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2848452	A1	20040618	FR 2002-15722	20021212

WO 2004062652 A1 20040729 WO 2003-FR3654 20031210
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2004138145 A1 20040715 US 2003-734787 20031212
PRIORITY APPLN. INFO.: FR 2002-15722 A 20021212
US 2003-455354P P 20030317

OTHER SOURCE(S): MARPAT 141:17641

AB The invention describe the application of the intestinal biliary acid reuptake inhibitors for the prevention and the treatment of Alzheimer's disease, alone or in conjunction with an HMG-CoA reductase inhibitor , a cholesterol uptake inhibitor, a cholesterol synthesis inhibitor or an inhibitor of APP secretases.

IT **252047-40-8**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and compns. for prevention and treatment of Alzheimer's disease with intestinal bile acid reuptake inhibitors)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 4 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:153577 HCAPLUS
DOCUMENT NUMBER: 140:350330
TITLE: A novel class of apical sodium-dependent bile acid transporter inhibitors: the amphiphilic 4-oxo-1-phenyl-1,4-dihydroquinoline derivatives
AUTHOR(S): Kurata, Hitoshi; Suzuki, Sayaka; Ohhata, Yasuo; Ikeda, Takuya; Hasegawa, Toru; Kitayama, Ken; Inaba, Toshimori; Kono, Keita; Kohama, Takafumi
CORPORATE SOURCE: Research Laboratories, Sankyo Co., Ltd, Hiromachi, Shinagawa-ku, Tokyo, 140-8710, Japan
SOURCE: Bioorganic & Medicinal Chemistry Letters (2004), 14(5), 1183-1186
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of 4-oxo-1-phenyl-1,4-dihydroquinolines possessing a linker and an ammonio moiety were synthesized and found to inhibit the apical sodium-dependent bile acid transporter (ASBT). The potency of ASBT inhibition varied with the position and length of the linking tether. Compound 21e effectively lowered the total serum cholesterol levels in hamsters.

IT **228113-66-4**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(amphiphilic hydroquinoline derivs. as apical sodium-dependent bile acid transporter inhibitors)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 5 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:938456 HCAPLUS
DOCUMENT NUMBER: 140:228927
TITLE: SC-435, an ileal apical sodium co-dependent bile acid

transporter (ASBT) inhibitor lowers plasma cholesterol and reduces atherosclerosis in guinea pigs
AUTHOR(S): West, Kristy L.; Zern, Tosca L.; Butteiger, Dustie N.; Keller, Bradley T.; Fernandez, Maria Luz
CORPORATE SOURCE: Department of Nutritional Sciences, University of Connecticut, Storrs, CT, 06269, USA
SOURCE: Atherosclerosis (Amsterdam, Netherlands) (2003), 171(2), 201-210
CODEN: ATHSBL; ISSN: 0021-9150
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Male Hartley guinea pigs were randomly allocated to one of four treatments, 10 guinea pigs per group, for 12 wk. The control diet contained no ASBT inhibitor (ASBTi) or simvastatin. Low ASBTi (LowASBTi) and high ASBTi (HighASBTi) were monotherapies containing 0.03 g/100 g and 0.1 g/100 g of the ASBTi SC-435. Combination therapy (COMBO) was a combination therapy consisting of 0.03 g/100 g ASBTi and 0.05 g/100 g simvastatin. Based on food consumption, guinea pigs received 17.2 and 47.8 mg/kg per day ASBTi in the ASBTi groups or 13.7 mg/kg per day ASBTi and 21.4 mg/kg per day simvastatin in the COMBO group. The amount of cholesterol in each diet was 0.25 g/100 g. LDL cholesterol was 40 and 70% lower with the HighASBTi and COMBO treatments compared to controls. Plasma triglycerides (TG) were 70% lower with COMBO therapy while HDL cholesterol was 43-47% higher with all treatments. Hepatic free cholesterol was reduced 60-80% with all treatments. Cholesterol content in the aortic arch was reduced by 25 and 42% in the HighASBTi and COMBO groups. Fecal bile acids were increased by 2.5- and 4-fold with HighASBTi and COMBO treatments. These data suggest that the interruption in the enterohepatic circulation of bile acids by ASBTi and statin co-administration therapy cause a significant reduction in plasma cholesterol concns. and attenuate the progression of atherosclerosis in guinea pigs.
IT **289037-67-8**, SC-435
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SC-435, an ileal apical sodium co-dependent bile acid transporter (ASBT) inhibitor lowers plasma cholesterol and reduces atherosclerosis in guinea pigs)
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:788415 HCAPLUS
DOCUMENT NUMBER: 140:139154
TITLE: Inhibition of ileal bile acid transport and reduced atherosclerosis in apoE-/- mice by SC-435
AUTHOR(S): Bhat, B. Ganesh; Rapp, Stephen R.; Beaudry, Judith A.; Napawan, Nida; Butteiger, Dustie N.; Hall, Kerri A.; Null, Christopher L.; Luo, Yi; Keller, Bradley T.
CORPORATE SOURCE: Cardiovascular and Metabolic Diseases Discovery Research, Pfizer Inc., St. Louis, MO, 63167, USA
SOURCE: Journal of Lipid Research (2003), 44(9), 1614-1621
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: American Society for Biochemistry and Molecular Biology, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Blocking intestinal bile acid absorption by inhibiting the apical sodium codependent bile acid transporter (ASBT) is a target for increasing hepatic bile acid synthesis and reducing plasma LDL cholesterol. SC-435 was identified as a potent inhibitor of ASBT (IC50 = 1.5 nM) in cells transfected with the human ASBT gene. Dietary administration of 3 mg/kg to 30 mg/kg SC-435 to apolipoprotein E-/- (apoE-/-) mice increased fecal

bile acid excretion by >2.5-fold. In vivo inhibition of ASBT also resulted in significant increases of hepatic mRNA levels for cholesterol 7α-hydroxylase and HMG-CoA reductase. Administration of 10 mg/kg SC-435 for 12 wk to apoE-/- mice lowered serum total cholesterol by 35% and reduced aortic root lesion area by 65%. Treatment of apoE-/- mice also resulted in decreased expression of ileal bile acid binding protein and hepatic nuclear hormone receptor small heterodimer partner, direct target genes of the farnesoid X receptor (FXR), suggesting a possible role of FXR in SC-435 modulation of cholesterol homeostasis. In dogs, SC-435 treatment reduced serum total cholesterol levels by ≤12% and, in combination with atorvastatin treatment, caused an addnl. reduction of 25%. These results suggest that specific inhibition of ASBT is a novel therapeutic approach for treatment of hypercholesterolemia resulting in a decreased risk for atherosclerosis.

IT **289037-67-8**, SC-435
RL: DMA (Drug mechanism of action); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of ileal bile acid transport and reduced atherosclerosis in apoE-/- mice by SC-435)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 7 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:430972 HCAPLUS
DOCUMENT NUMBER: 139:224179
TITLE: Inhibition of both the apical sodium-dependent bile acid transporter and HMG-CoA reductase markedly enhances the clearance of LDL apoB
AUTHOR(S): Telford, Dawn E.; Edwards, Jane Y.; Lipson, Sara M.; Sutherland, Brian; Barrett, P. Hugh R.; Burnett, John R.; Krul, Elaine S.; Keller, Bradley T.; Huff, Murray W.
CORPORATE SOURCE: Robarts Research Institute and Departments of Medicine and Biochemistry, University of Western Ontario, London, ON, Can.
SOURCE: Journal of Lipid Research (2003), 44(5), 943-952
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: Lipid Research, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Discovery of the ileal apical sodium-dependent bile acid transporter (ASBT) permitted development of specific inhibitors of bile acid resorption, potentially a new class of cholesterol-lowering agents. In the present study, we tested the hypothesis that combining the novel ASBT inhibitor, SC-435, with the HMG-CoA reductase inhibitor, atorvastatin, would potentiate redns. in LDL cholesterol (LDL-C) and LDL apolipoprotein B (apoB). ApoB kinetic studies were performed in miniature pigs fed a typical human diet and treated with the combination of SC-435 (5 mg/kg/day) plus atorvastatin (3 mg/kg/day) (SC-435+A) or a placebo. SC-435+A decreased plasma total cholesterol by 23% and LDL-C by 40%. Multicompartmental anal. (SAAM II) demonstrated that LDL apoB significantly decreased by 35% due primarily to a 45% increase in the LDL apoB fractional catabolic rate (FCR). SC-435+A significantly decreased hepatic concns. of free cholesterol and cholesteryl ester, and increased hepatic LDL receptor mRNA consequent to increased cholesterol 7α-hydroxylase expression and activity. In comparison, SC-435 (10 mg/kg/day) monotherapy decreased LDL apoB by 10% due entirely to an 18% increase in LDL apoB FCR, whereas atorvastatin monotherapy (3 mg/kg/day) decreased LDL apoB by 30% due primarily to a 22% reduction in LDL apoB production We conclude that SC-435+A potentiates the reduction of LDL-C and LDL apoB due to complementary mechanisms of action.

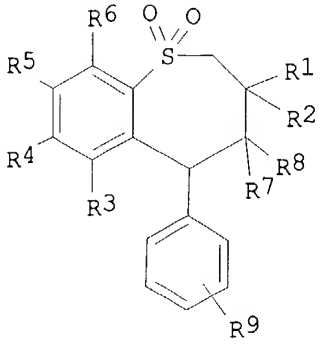
IT **289037-67-8**, SC 435
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(inhibition of both the apical sodium-dependent bile acid transporter and HMG-CoA reductase markedly enhances the clearance of LDL apoB)
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 8 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:221671 HCAPLUS
DOCUMENT NUMBER: 138:238032
TITLE: Preparation of benzothiepine derivatives for potential use as ileal bile acid transport inhibitors for the treatment of hyperlipidemia
INVENTOR(S): Starke, Ingemar; Dahlstrom, Mikael Ulf Johan; Blomberg, David
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; Astrazeneca UK Limited
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003022830	A1	20030320	WO 2002-GB4029	20020905
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1427718	A1	20040616	EP 2002-765012	20020905
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002012345	A	20040810	BR 2002-12345	20020905
PRIORITY APPLN. INFO.:			GB 2001-21622 A	20010907
			WO 2002-GB4029 W	20020905

OTHER SOURCE(S): MARPAT 138:238032
GI



I

AB Benzothiepines I, wherein R1 and R2 are selected from hydrogen, alkyl, alkenyl, and the other is selected from alkyl, alkenyl; R3 and R6 and the other of R4 and R5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkanoyloxy, N-(alkyl)amino, N,N-(alkyl)2amino, alkanoylamino, N-(alkyl)carbamoyl, N,N-(alkyl)2carbamoyl, alkyl-S(O)a wherein a is 0 to 2, alkoxycarbonyl, N-(alkyl)sulphamoyl and N,N-(alkyl)2sulphamoyl; wherein R3 and R6 and the other of R4 and R5 may be optionally substituted on carbon; R7 and R8 are independently H, OH, amino, mercapto, alkyl, alkoxy, alkyl-S(O)a wherein a is 0 to 2; R9 is (Rz)v; Rz is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkanoyloxy, N-(alkyl)amino, N,N-(alkyl)2amino, alkanoylamino, N-(alkyl)carbamoyl, N,N-(alkyl)2carbamoyl, alkyl-S(O)a wherein a is 0 to 2, alkoxycarbonyl, N-(alkyl)sulphamoyl and N,N-(alkyl)2sulphamoyl; v is 0-5; variable groups are as defined within; pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof and their potential use as ileal bile acid transport (IBAT) inhibitors for the treatment of hyperlipidemia. Processes for their manufacture and pharmaceutical compns. containing them are also described. Thus, 1,1-Dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(N-{(R)-α-[N-(carboxymethyl)carbamoyl]benzyl}carbamoylmethylthio)-2,3,4,5-tetrahydro-1,4-benzothiepine was prepared and tested as ileal bile acid transport inhibitor and for the treatment of hyperlipidemia (no data).

IT **501923-60-0P**
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of benzothiepine derivs. for potential use as ileal bile acid transport inhibitors for the treatment of hyperlipidemia)

IT **501923-58-6P 501923-59-7P 501947-90-6P 501947-91-7P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of benzothiepine derivs. for potential use as ileal bile acid transport inhibitors for the treatment of hyperlipidemia)

IT **501923-61-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of benzothiepine derivs. for potential use as ileal bile acid transport inhibitors for the treatment of hyperlipidemia)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:221650 HCAPLUS
DOCUMENT NUMBER: 139:323443
TITLE: Method for the preparation and recrystallization of crystalline tetrahydrobenzothiepinedioxides of high purity
INVENTOR(S): Mudipalli, Partha S.; Pozzo, Mark J.; Park, Jung Min
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: PCT Int. Appl., 208 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003022804	A2	20030320	WO 2002-US26877	20020823
WO 2003022804	C2	20031218		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003199515	A1	20031023	US 2002-226229	20020823
EP 1425279	A2	20040609	EP 2002-798091	20020823

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

PRIORITY APPLN. INFO.: US 2001-318334P P 20010912
WO 2002-US26877 W 20020823

OTHER SOURCE(S): MARPAT 139:323443

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides an improved process for the preparation of single crystals of apical sodium co-dependent bile acid transport (ASBT) inhibitors I•X- [wherein R1 and R2 = hydrocarbyl; R3-R5 = independently H or hydrocarbyl optionally interrupted by O, N, or S; or 2 or more R3-R5 taken together with the atom to which they are attached form a cyclic moiety; R9 = H, hydrocarbyl, hydroxyalkyl, (poly)alkoxyalkyl, (alkyl)aminoalkyl, amminioalkyl, (quaternary) heterocyclyl, (quaternary) heteroaryl, OR3, NR3R4, NR4R4R5+A-, SR3, SOR3, SO2R3, SO3R3, oxo, CO2R3, CN, halo, NCO, CONR3R4, SO2M, SO2NR3R4, PO(OR23)OR24, PR3R4R5+A-, SR3R4+A-, or CO2M; R23 and R24 = independently R3 or M; n = 0-4; X- and A- = pharmaceutically acceptable anions; M = pharmaceutically acceptable cations; and enantiomers thereof] having purity ≥ 99% by weight and levels of solvent impurities ≤ 1%. The recrystn. process comprises the steps of (1) solubilizing the compound under an inert atmospheric in a solvent system of H2O and a water-miscible solvent, e.g. acetone, acetonitrile, Me Et ketone, or THF, with optional addition of a basic additive, (2) adjusting the H2O concentration from about 0.5% to about 7% by volume in the solvent system under an inert atmospheric to recrystallize the compound, and (3) separating the non-hygroscopic single crystal from the solvent system. In addition, the complete synthesis of the ASBT inhibitor (4R,5R)-II•Cl- in a multi-step sequence starting from 2-chloro-5-nitrobenzoic acid, anisole, and di-Et dibutylmalonate is given. The synthesis involves the cyclization of the 1-(2,2-dibutyl-3-oxopropylsulfonyl)-2-[(4-methoxyphenyl)methyl]-4-dimethylaminobenzene intermediate (89%) and resolution of the resulting tetrahydrobenzothiepinedioxide, followed by further substitution. Two crystalline forms of (4R,5R)-II•Cl- are characterized by a number of means, including X-ray powder diffraction, differential scanning calorimetry profiles, and water sorption isotherms. A detailed recrystn. procedure with various options, giving yields of ≥85% and purity of ≥99.0%, is also described.

IT **197373-42-5P**, cis-3,3-Dibutyl-7-(dimethylamino)-1,1-dioxido-4-hydroxy-5-(4-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine
RL: IMF (Industrial manufacture); PEP (Physical, engineering or chemical process); PYP (Physical process); PREP (Preparation); PROC (Process)
(intermediate; preparation and recrystn. of crystalline tetrahydrobenzothiepinedioxides of high purity)

IT **228113-64-2P**, (4R,5R)-3,3-Dibutyl-7-(dimethylamino)-1,1-dioxido-4-hydroxy-5-(4-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine
361373-74-2P, (4S,5S)-3,3-Dibutyl-7-(dimethylamino)-1,1-dioxido-4-hydroxy-5-(4-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine

RL: IMF (Industrial manufacture); PUR (Purification or recovery); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation and recrystn. of crystalline tetrahydrobenzothiepinedioxides of high purity)

IT **228113-65-3P**, (4R,5R)-3,3-Dibutyl-7-(dimethylamino)-1,1-dioxido-4-hydroxy-5-(4-hydroxyphenyl)-2,3,4,5-tetrahydrobenzothiepine
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation and recrystn. of crystalline tetrahydrobenzothiepinedioxides of high purity)

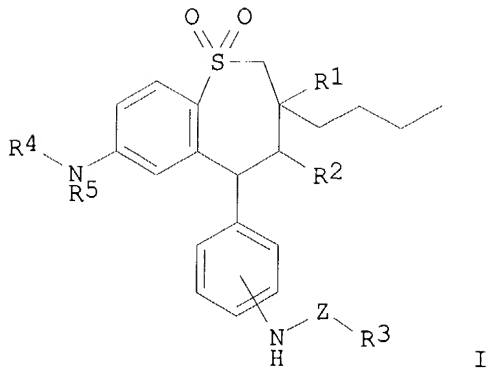
IT **228113-66-4P**
RL: IMF (Industrial manufacture); PRP (Properties); PUR (Purification or recovery); PREP (Preparation)
(preparation and recrystn. of crystalline tetrahydrobenzothiepinedioxides of high purity)

IT **289038-78-4**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and recrystn. of crystalline tetrahydrobenzothiepinedioxides of high purity)

L20 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:173440 HCAPLUS
DOCUMENT NUMBER: 138:215326
TITLE: Combined preparations, containing 1,4-benzothiepine-1,1-dioxide derivatives and other active substances for the treatment of hyperlipidemia
INVENTOR(S): Glombik, Heiner; Frick, Wendelin; Schaefer, Hans-Ludwig; Kramer, Werner
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003018024	A1	20030306	WO 2002-EP8908	20020809
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10140169	A1	20030306	DE 2001-10140169	20010822
DE 10142456	A1	20030320	DE 2001-10142456	20010831
EP 1425018	A1	20040609	EP 2002-796213	20020809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002012031	A	20040803	BR 2002-12031	20020809
PRIORITY APPLN. INFO.:			DE 2001-10140169 A	20010822
			DE 2001-10142456 A	20010831
			WO 2002-EP8908 W	20020809

OTHER SOURCE(S): MARPAT 138:215326
GI



I

AB The invention relates to mixts. of substances, containing 1,4-benzothiepine-1,1-dioxide derivs. of formula (I), in which the functional groups have the indicated meanings, their physiol. acceptable salts and physiol. functional derivs. as well as other active substances for the treatment of metabolic disorders especially hyperlipidemia. The combinations can also include antidiabetics, antiarthrytics etc. A typical capsule contains 100 mg of the drugs and 400 mg triglyceride mixture from coco fatty acids; other formulations are emulsions, tablets, dragees, and solns. Hamster that were fed with cholesterol-rich feed received orally the drug combination once daily for 10 days. Feces was analyzed for bile acids, blood lipid levels were measured and cholesterol was determined from liver.

IT **252047-40-8**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:827165 HCAPLUS
DOCUMENT NUMBER: 138:362455
TITLE: Inhibition of the apical sodium-dependent bile acid transporter reduces LDL cholesterol and apoB by enhanced plasma clearance of LDL apoB
AUTHOR(S): Huff, Murray W.; Telford, Dawn E.; Edwards, Jane Y.; Burnett, John R.; Barrett, P. Hugh R.; Rapp, Stephen R.; Napawan, Nida; Keller, Bradley T.
CORPORATE SOURCE: Dep. Med. and Biochem., The University of Western Ontario, London, ON, Can.
SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology (2002), 22(11), 1884-1891
CODEN: ATVBFA; ISSN: 1079-5642
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective-Cloning of the ileal apical sodium-dependent bile acid transporter (ASBT) has identified a new pharmacol. target for the modulation of plasma lipoproteins. The objective of this study was to determine whether a novel, specific, minimally absorbed ASBT inhibitor (SC-435) decreases LDL cholesterol through the alteration of plasma apoB kinetics. Methods and Results-Miniature pigs were treated for 21 days with 10 mg/kg/day of SC-435 of placebo. SC-435 decreased plasma cholesterol by 9% and LDL cholesterol by 20% with no effect on other lipids. Autologous 131I-VLDL, 125I-LDL, and [3H]-leucine were injected simultaneously to determine apoB kinetics. LDL apoB concns. decreased significantly by 10% resulting

entirely from an increase in LDL-apoB fractional catabolic rate. SC-435 had no effect on either total LDL apoB production or VLDL apoB converted to LDL. SC-435 increased VLDL apoB production by 22%; however, the concentration was unchanged as a result of increased VLDL apoB direct removal. SC-435 increased hepatic mRNA and enzymic activity for both cholesterol 7α-hydroxylase and HMG-CoA reductase. Conclusions-A low dose of the ASBT inhibitor, SC-435, significantly reduces plasma LDL cholesterol through enhanced LDL receptor-mediated LDL apoB clearance, secondary to increased expression of cholesterol 7α-hydroxylase.

IT **289037-67-8**, SC 435
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of apical sodium-dependent bile acid transporter reduces LDL cholesterol and apoB by enhanced plasma clearance of LDL apoB)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 12 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:749934 HCAPLUS
DOCUMENT NUMBER: 138:314263
TITLE: 1-[4-[4[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]butyl]-4-aza-1-azoniabicyclo[2.2.2]octane methanesulfonate (SC-435), an ileal apical sodium-codependent bile acid transporter inhibitor alters hepatic cholesterol metabolism and lowers plasma low-density lipoprotein-cholesterol concentrations in guinea pigs
AUTHOR(S): West, Kristy L.; Ramjiganesh, Tripurasundari; Roy, Suheeta; Keller, Bradley T.; Fernandez, Maria Luz
CORPORATE SOURCE: Department of Nutritional Sciences, University of Connecticut, Storrs, CT, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2002), 303(1), 293-299
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Male Hartley guinea pigs (10/group) were assigned either to a control diet (no drug treatment) or to diets containing 0.4, 2.2, or 7.3 mg/day of an ileal apical sodium-codependent bile acid transporter (ASBT) inhibitor, SC-435. Based on food consumption, guinea pigs received 0, 0.8, 3.7, or 13.4 mg/kg/day of the ASBT inhibitor. The amount of cholesterol in the four diets was maintained at 0.17%, equivalent to 1200 mg/day in the human situation. Guinea pigs treated with 13.4 mg/kg/day SC-435 had 41% lower total cholesterol and 44% lower low-d. lipoprotein (LDL)-cholesterol concns. compared with control ($P < 0.01$), whereas no significant differences were observed with either of the lower doses of SC-435. Hepatic cholesterol esters were significantly reduced by 43, 56, and 70% in guinea pigs fed 0.8, 3.7, and 13.4 mg/kg/day of the ASBT inhibitor, resp. ($P < 0.01$). In addition, the highest dose of the inhibitor resulted in a 42% increase in the number of very low-d. lipoprotein (VLDL) triacylglycerol mols. and a larger VLDL diameter compared with controls ($P < 0.05$). Acyl-CoA cholesterol/acyltransferase activity was 30% lower with the highest dose treatment, whereas cholesterol 7α-hydroxylase, the regulatory enzyme of bile acid synthesis, was 30% higher with the highest ASBT inhibitor dose ($P < 0.05$). Furthermore, bile acid excretion increased 2-fold with the highest dose of SC-435 compared with the control group ($P < 0.05$). These results suggest that the reduction in total and LDL-cholesterol concns. by the ASBT inhibitor is a result of alterations in hepatic cholesterol metabolism due to modifications in the enterohepatic circulation of bile acids.

IT **289037-67-8**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SC-435, a bile acid transporter inhibitor, alters hepatic cholesterol metabolism and lowers plasma LDL-cholesterol levels in guinea pigs)
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 13 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:716126 HCAPLUS
DOCUMENT NUMBER: 137:252985
TITLE: Medicinal compositions containing bile acid transporter inhibitor and cholesterol acyltransferase inhibitors
INVENTOR(S): Inaba, Toshimori
PATENT ASSIGNEE(S): Sankyo Company, Limited, Japan
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002072147	A1	20020919	WO 2002-JP2311	20020312
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2002338496	A2	20021127	JP 2002-67841	20020313
PRIORITY APPLN. INFO.:			JP 2001-72050 A	20010314

AB Disclosed are medicinal compns. for administering an ileal bile acid transporter inhibitor and a cholesterol acyltransferase (ACAT) inhibitor either at the same time or sep. at a certain interval. The effect of oral administration of both 4-[3-[(1-(3,5-difluorophenyl)ethylamino)-(4-methoxyphenyl)methyl]phenylamino]-3-hydroxy-3-cyclobutene-1,2-dione (I) and N-(1-octyl-5-carboxymethyl-4,6-dimethylindoline-7-yl)-2,2-dimethylpropaneamide (II) on blood serum triglyceride was prepared Also, a tablet containing I 50, II 30, lactose 368, corn starch 50, magnesium stearate 2 mg was prepared

IT **460041-92-3 460041-93-4 460041-94-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hypolipemic compns. containing bile acid transporter inhibitor and cholesterol acyltransferase inhibitors)
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 14 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:487559 HCAPLUS
DOCUMENT NUMBER: 137:63115
TITLE: Preparation of diphenylazetidinone derivatives as hypolipidemic agents
INVENTOR(S): Glombik, Heiner; Kramer, Werner; Flohr, Stefanie; Frick, Wendelin; Heuer, Hubert; Jaehne, Gerhard; Lindenschmidt, Andreas; Schaefer, Hans-Ludwig
PATENT ASSIGNEE(S): Aventis Pharma Deutschland GmbH, Germany

SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002050068	A1	20020627	WO 2001-EP14532	20011211
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10064402	A1	20020627	DE 2000-10064402	20001221
DE 10154520	A1	20031002	DE 2001-10154520	20011107
AU 2002019173	A5	20020701	AU 2002-19173	20011211
EE 200300237	A	20030815	EE 2003-237	20011211
EP 1345932	A1	20030924	EP 2001-271371	20011211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001016482	A	20040203	BR 2001-16482	20011211
JP 2004516293	T2	20040603	JP 2002-551564	20011211
US 2002128252	A1	20020912	US 2001-21028	20011219
US 6498156	B2	20021224		
NO 2003002733	A	20030814	NO 2003-2733	20030616

PRIORITY APPLN. INFO.:

DE 2000-10064402	A	20001221
DE 2001-10154520	A	20011107
WO 2001-EP14532	W	20011211

OTHER SOURCE(S): MARPAT 137:63115
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The compds. are suited for use e.g. as hypolipidemic drugs. The invention discloses preparation of diphenylazetidinone derivs. such as I [R1, R2, R3, R4, R5, R6 = C0-C30-alkylene-L {optionally containing O, CO, CH:CH, C.tplbond.C, N(alkyl), N(alkylphenyl), NH}, H, F, Cl, Br, I, CF3, NO2, CN, CO2H, CO2(alkyl), CONH2, CONH(alkyl), CON(alkyl)2, alkyl, alkenyl, alkynyl, O-alkyl, SO2NH2, SO2NH(alkyl) SO2N(alkyl)2, S-(alkyl), SO(alkyl), (un)substituted S(CH2)nPh, SO(CH2)nPh, SO2(alkyl), SO2(CH2)nPh, NH2, NH(alkyl), N(alkyl)2, NH(acyl), (un)substituted Ph, O(CH2)nPh; n = 0-6; L = II; R7, R9, R10 = Me, Et, Pr, butyl; R8 = H, OH, NH2, NH(alkyl)], and their physiol. acceptable salts, for their use as hypolipidemic agents. Thus, 1,2-diphenylazetidinone derivative III·trifluoroacetate (IV) was prepared via a multistep synthetic sequence starting from 7-[3-(3-butyl-7-dimethylamino-3-ethyl-4-hydroxy-1,1-dioxo-2,3,4,5-tetrahydro-1H-benzo[b]thiepin-5-yl)-phenylcarbamoyl]-heptanoic acid and 4-(4-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxyphenyl]-azetidin-2-one. Azetidinone IV was tested for its cholesterol lowering ability [ED50 = 0.01 mg/mouse].

IT **439113-82-3P 439113-89-0P 439113-91-4P**
439113-92-5P 439113-93-6P 439113-96-9P
439113-98-1P 439114-01-9P 439114-03-1P
439114-06-4P 439114-08-6P 439114-11-1P

439114-16-6P 439114-20-2P 439114-22-4P
439114-23-5P 439114-26-8P 439114-29-1P
439114-36-0P 439114-38-2P 439114-39-3P
439114-40-6P 439120-25-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of diphenylazetidinone derivs. as hypolipidemics)

IT **439114-09-7 439114-42-8 439114-43-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of diphenylazetidinone derivs. as hypolipidemics)

IT **439113-88-9P 439113-94-7P 439113-99-2P**
439114-04-2P 439114-14-4P 439114-18-8P
439114-24-6P 439114-27-9P 439114-32-6P
439114-34-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of diphenylazetidinone derivs. as hypolipidemics)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 15 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:456926 HCAPLUS
DOCUMENT NUMBER: 133:84286
TITLE: Combinations of ileal bile acid transport inhibitors and nicotinic acid derivatives for cardiovascular indications
INVENTOR(S): Keller, Bradley T.; Glenn, Kevin C.; Connolly, Daniel T.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000038729	A1	20000706	WO 1999-US27950	19991217
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2356664	AA	20000706	CA 1999-2356664	19991217
EP 1140191	A1	20011010	EP 1999-967141	19991217
EP 1140191	B1	20021023		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9916567	A	20011211	BR 1999-16567	19991217
JP 2002533415	T2	20021008	JP 2000-590680	19991217
AT 226448	E	20021115	AT 1999-967141	19991217
EP 1293211	A1	20030319	EP 2002-25631	19991217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
ES 2188285	T3	20030616	ES 1999-967141	19991217
EP 1336413	A1	20030820	EP 2003-9706	19991217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

	IE, FI, RO, CY				
EP 1340508		A1	20030903	EP 2003-12143	19991217
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
EP 1340509		A1	20030903	EP 2003-12144	19991217
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
EP 1340510		A1	20030903	EP 2003-12145	19991217
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
EP 1342475		A1	20030910	EP 2003-11146	19991217
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
EP 1354604		A1	20031022	EP 2003-16600	19991217
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
NZ 512533		A	20040227	NZ 1999-512533	19991217
NO 2001003160		A	20010821	NO 2001-3160	20010622
US 2003166720		A1	20030904	US 2002-200600	20020723
US 2003203892		A1	20031030	US 2002-200599	20020723
US 2003109558		A1	20030612	US 2002-245506	20020918
US 2003125316		A1	20030703	US 2002-245507	20020918
US 2004058908		A1	20040325	US 2002-266743	20021009
US 2004029845		A1	20040212	US 2003-373180	20030226
US 2004028644		A1	20040212	US 2003-412694	20030414
US 2004048846		A1	20040311	US 2003-652306	20030902
PRIORITY APPLN. INFO.:				US 1998-113955P	P 19981223
				US 1999-142550P	P 19990707
				US 1999-142603P	P 19990707
				US 1999-142616P	P 19990707
				US 1999-142682P	P 19990707
				US 1999-142684P	P 19990707
				US 1999-143043P	P 19990707
				US 1999-143047P	P 19990707
				US 1999-143550P	P 19990713
				EP 1999-965035	A3 19991217
				EP 1999-965899	A3 19991217
				EP 1999-965900	A3 19991217
				EP 1999-965901	A3 19991217
				EP 1999-965902	A3 19991217
				EP 1999-965903	A3 19991217
				EP 1999-967140	A3 19991217
				US 1999-465642	A3 19991217
				US 1999-466413	A3 19991217
				US 1999-466415	A3 19991217
				US 1999-466466	B1 19991217
				US 1999-466469	A3 19991217
				US 1999-466470	A3 19991217
				US 1999-466592	A3 19991217
				US 1999-466596	B3 19991217
				WO 1999-US27950	W 19991217

AB Combinations of cardiovascular therapeutic compds. are provided for the prophylaxis or treatment of cardiovascular disease including hypercholesterolemia, atherosclerosis, or hyperlipidemia. Combinations disclosed include an ileal bile acid transport inhibitor combined with a nicotinic acid derivative

IT **197373-42-5 197373-42-5D**, enantiomers
280105-79-5 280105-79-5D, enantiomers
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ileal bile acid transport inhibitor-nicotinic acid derivative combination for cardiovascular indications)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 16 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:456925 HCAPLUS
DOCUMENT NUMBER: 133:94516
TITLE: Combinations of ileal bile acid transport inhibitors and bile acid sequestering agents for cardiovascular indications
INVENTOR(S): Keller, Bradley T.; Glenn, Kevin C.; Schuh, Joseph R.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000038728	A1	20000706	WO 1999-US27949	19991217
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2356156	AA	20000706	CA 1999-2356156	19991217
EP 1140190	A1	20011010	EP 1999-967140	19991217
EP 1140190	B1	20021120		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9916484	A	20020122	BR 1999-16484	19991217
JP 2002533414	T2	20021008	JP 2000-590679	19991217
AT 228012	E	20021215	AT 1999-967140	19991217
EP 1293211	A1	20030319	EP 2002-25631	19991217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
US 6562860	B1	20030513	US 1999-466592	19991217
ES 2189529	T3	20030701	ES 1999-967140	19991217
EP 1336413	A1	20030820	EP 2003-9706	19991217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
EP 1340508	A1	20030903	EP 2003-12143	19991217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
EP 1340509	A1	20030903	EP 2003-12144	19991217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
EP 1340510	A1	20030903	EP 2003-12145	19991217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
EP 1342475	A1	20030910	EP 2003-11146	19991217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
EP 1354604	A1	20031022	EP 2003-16600	19991217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
NZ 512535	A	20031219	NZ 1999-512535	19991217
NO 2001003159	A	20010822	NO 2001-3159	20010622

US 2003166720	A1	20030904	US 2002-200600		20020723
US 2003203892	A1	20031030	US 2002-200599		20020723
US 2003109558	A1	20030612	US 2002-245506		20020918
US 2003125316	A1	20030703	US 2002-245507		20020918
US 2004058908	A1	20040325	US 2002-266743		20021009
US 2004029845	A1	20040212	US 2003-373180		20030226
US 2004028644	A1	20040212	US 2003-412694		20030414
US 2004048846	A1	20040311	US 2003-652306		20030902
PRIORITY APPLN. INFO.:			US 1998-113955P	P	19981223
			US 1999-143043P	P	19990707
			US 1999-142603P	P	19990707
			US 1999-142616P	P	19990707
			US 1999-142682P	P	19990707
			US 1999-142684P	P	19990707
			US 1999-143047P	P	19990707
			US 1999-143550P	P	19990713
			EP 1999-965035	A3	19991217
			EP 1999-965899	A3	19991217
			EP 1999-965900	A3	19991217
			EP 1999-965901	A3	19991217
			EP 1999-965902	A3	19991217
			EP 1999-965903	A3	19991217
			EP 1999-967140	A3	19991217
			US 1999-465642	A3	19991217
			US 1999-466413	A3	19991217
			US 1999-466415	A3	19991217
			US 1999-466466	B1	19991217
			US 1999-466469	A3	19991217
			US 1999-466470	A3	19991217
			US 1999-466592	A3	19991217
			US 1999-466596	B3	19991217
			WO 1999-US27949	W	19991217

AB The present invention provides combinations of cardiovascular therapeutic compds. for the prophylaxis or treatment of cardiovascular disease including hypercholesterolemia, atherosclerosis, or hyperlipidemia. Combinations disclosed include an ileal bile acid transport inhibitor combined with a bile acid sequestrant. A therapeutic combination containing (3R,5R)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1-4-benzothiazepine-1,2-dioxide and cholestyramine is disclosed. Different biol. assays to show the utility of the invention are described.

IT **197373-42-5D**, enantiomers, mixture with sequestering agents
280105-79-5D, enantiomers, mixture with sequestering agents
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations of ileal bile acid transport inhibitors and bile acid sequestering agents for cardiovascular indications)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 17 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:456924 HCAPLUS
DOCUMENT NUMBER: 133:79370
TITLE: Combinations of ileal bile acid transport inhibitors and fibric acid derivatives for cardiovascular indications
INVENTOR(S): Keller, Bradley T.; Glenn, Kevin C.; Schuh, Joseph R.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000038727	A1	20000706	WO 1999-US27948		19991217
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2356607	AA	20000706	CA 1999-2356607		19991217
EP 1140189	A1	20011010	EP 1999-965903		19991217
EP 1140189	B1	20030514			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
BR 9916565	A	20020129	BR 1999-16565		19991217
JP 2002533413	T2	20021008	JP 2000-590678		19991217
EP 1293211	A1	20030319	EP 2002-25631		19991217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY					
AT 240120	E	20030515	AT 1999-965903		19991217
EP 1336413	A1	20030820	EP 2003-9706		19991217
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EP 1340508	A1	20030903	EP 2003-12143		19991217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY					
EP 1340509	A1	20030903	EP 2003-12144		19991217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY					
EP 1340510	A1	20030903	EP 2003-12145		19991217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY					
EP 1342475	A1	20030910	EP 2003-11146		19991217
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PT 1140189	T	20030930	PT 1999-965903		19991217
EP 1354604	A1	20031022	EP 2003-16600		19991217
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US 6638969	B1	20031028	US 1999-465642		19991217
NZ 512537	A	20031128	NZ 1999-512537		19991217
ES 2200588	T3	20040301	ES 1999-965903		19991217
NO 2001003162	A	20010821	NO 2001-3162		20010622
HK 1040926	A1	20031017	HK 2002-102722		20020410
US 2003166720	A1	20030904	US 2002-200600		20020723
US 2003203892	A1	20031030	US 2002-200599		20020723
US 2003109558	A1	20030612	US 2002-245506		20020918
US 2003125316	A1	20030703	US 2002-245507		20020918
US 2004058908	A1	20040325	US 2002-266743		20021009
US 2004029845	A1	20040212	US 2003-373180		20030226
US 2004028644	A1	20040212	US 2003-412694		20030414
US 2004048846	A1	20040311	US 2003-652306		20030902
PRIORITY APPLN. INFO.:			US 1998-113955P	P	19981223
			US 1999-142603P	P	19990707
			US 1999-142616P	P	19990707
			US 1999-142682P	P	19990707
			US 1999-142684P	P	19990707
			US 1999-143043P	P	19990707

US 1999-143047P	P	19990707
US 1999-143550P	P	19990713
EP 1999-965035	A3	19991217
EP 1999-965899	A3	19991217
EP 1999-965900	A3	19991217
EP 1999-965901	A3	19991217
EP 1999-965902	A3	19991217
EP 1999-965903	A3	19991217
EP 1999-967140	A3	19991217
US 1999-465642	A3	19991217
US 1999-466413	A3	19991217
US 1999-466415	A3	19991217
US 1999-466466	B1	19991217
US 1999-466469	A3	19991217
US 1999-466470	A3	19991217
US 1999-466592	A3	19991217
US 1999-466596	B3	19991217
WO 1999-US27948	W	19991217

AB The present invention provides combinations of cardiovascular therapeutic compds. for the prophylaxis or treatment of cardiovascular disease including hypercholesterolemia, atherosclerosis, or hyperlipidemia. Combinations disclosed include an ileal bile acid transport inhibitor combined with a fibric acid derivative A therapeutic combination containing (3R,5R)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1-4-benzothiazepine-1,2-dioxide and clofibrate is disclosed. Different biol. assays to show the utility of the invention are described.

IT **197373-42-5D**, enantiomers, mixts. with fibric acid derivs.
280105-79-5D, enantiomers, mixts. with fibric acid derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations of ileal bile acid transport inhibitors and fibric acid derivs. for cardiovascular indications)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 18 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:456923 HCAPLUS
DOCUMENT NUMBER: 133:79369
TITLE: Combinations of ileal bile acid transport inhibitors and cholesteryl ester transfer protein inhibitors for cardiovascular indications
INVENTOR(S): Keller, Bradley T.; Sikorski, James A.; Glenn, Kevin C.; Connolly, Daniel T.; Smith, Mark E.; Schuh, Joseph R.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000038726	A1	20000706	WO 1999-US27947	19991217

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,

DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2356422	AA	20000706	CA 1999-2356422	19991217
EP 1140188	A1	20011010	EP 1999-965902	19991217
EP 1140188	B1	20030528		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

BR 9916486	A	20020205	BR 1999-16486	19991217
US 6458851	B1	20021001	US 1999-466415	19991217
JP 2002533412	T2	20021008	JP 2000-590677	19991217
EP 1293211	A1	20030319	EP 2002-25631	19991217

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY

AT 241386	E	20030615	AT 1999-965902	19991217
EP 1336413	A1	20030820	EP 2003-9706	19991217

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY

EP 1340508	A1	20030903	EP 2003-12143	19991217

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY

EP 1340509	A1	20030903	EP 2003-12144	19991217

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY

EP 1340510	A1	20030903	EP 2003-12145	19991217

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY

EP 1342475	A1	20030910	EP 2003-11146	19991217

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY

EP 1354604	A1	20031022	EP 2003-16600	19991217

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY

PT 1140188	T	20031031	PT 1999-965902	19991217
NZ 512536	A	20031128	NZ 1999-512536	19991217
ES 2200587	T3	20040301	ES 1999-965902	19991217
NO 2001003161	A	20010817	NO 2001-3161	20010622
HK 1041443	A1	20030919	HK 2002-102732	20020410
US 2003166720	A1	20030904	US 2002-200600	20020723
US 2003203892	A1	20031030	US 2002-200599	20020723
US 2003109558	A1	20030612	US 2002-245506	20020918
US 2003125316	A1	20030703	US 2002-245507	20020918
US 2004058908	A1	20040325	US 2002-266743	20021009
US 2004029845	A1	20040212	US 2003-373180	20030226
US 2004028644	A1	20040212	US 2003-412694	20030414
US 2004048846	A1	20040311	US 2003-652306	20030902

PRIORITY APPLN. INFO.:

US 1998-113955P	P	19981223
US 1999-143047P	P	19990707
US 1999-142603P	P	19990707
US 1999-142616P	P	19990707
US 1999-142682P	P	19990707
US 1999-142684P	P	19990707
US 1999-143043P	P	19990707
US 1999-143550P	P	19990713
EP 1999-965035	A3	19991217
EP 1999-965899	A3	19991217
EP 1999-965900	A3	19991217
EP 1999-965901	A3	19991217
EP 1999-965902	A3	19991217
EP 1999-965903	A3	19991217
EP 1999-967140	A3	19991217
US 1999-465642	A3	19991217
US 1999-466413	A3	19991217
US 1999-466415	A3	19991217

US 1999-466466	B1	19991217
US 1999-466469	A3	19991217
US 1999-466470	A3	19991217
US 1999-466592	A3	19991217
US 1999-466596	B3	19991217
WO 1999-US27947	W	19991217

AB The present invention provides combinations of cardiovascular therapeutic compds. for the prophylaxis or treatment of cardiovascular disease including hypercholesterolemia, atherosclerosis, or hyperlipidemia. Combinations disclosed include an ileal bile acid transport inhibitor combined with a cholesteryl ester transfer protein (CETP) inhibitor. A therapeutic combination containing (3R,5R)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1-4-benzothiazepine-1,2-dioxide and a cholesteryl ester transfer protein inhibitor is disclosed. Different biol. assays to show the utility of the invention are described.

IT **197373-42-5D**, enantiomers **280105-79-5D**, enantiomers
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mixts. with cholesteryl ester transfer protein inhibitors; combinations of ileal bile acid transport inhibitors and cholesteryl ester transfer protein inhibitors for cardiovascular indications)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 19 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:795803 HCAPLUS
DOCUMENT NUMBER: 132:35625
TITLE: Amino acid containing benzo[b]thiepine 1,1-dioxide derivatives as hypolipemic agents
INVENTOR(S): Frick, Wendelin; Enhsen, Alfons; Glombik, Heiner; Heuer, Hubert
PATENT ASSIGNEE(S): Hoechst Marion Roussel Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964410	A1	19991216	WO 1999-EP3701	19990528
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19825804	A1	19991216	DE 1998-19825804	19980610
DE 19825804	C2	20000824		
CA 2334775	AA	19991216	CA 1999-2334775	19990528
AU 9945019	A1	19991230	AU 1999-45019	19990528
AU 753275	B2	20021010		
EP 1086092	A1	20010328	EP 1999-927784	19990528
EP 1086092	B1	20021113		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
BR 9912188	A	20010410	BR 1999-12188	19990528
TR 200003634	T2	20010621	TR 2000-200003634	19990528
JP 2002517491	T2	20020618	JP 2000-553419	19990528

AT 227715	E	20021115	AT 1999-927784	19990528
ES 2182535	T3	20030301	ES 1999-927784	19990528
PT 1086092	T	20030331	PT 1999-927784	19990528
RU 2215001	C2	20031027	RU 2001-101491	19990528
TR 200003632	T2	20010420	TR 2000-200003632	19990529
AU 761249	B2	20030529	AU 2000-53394	20000816
ZA 2000007060	A	20010718	ZA 2000-7060	20001130
ZA 2000007061	A	20010718	ZA 2000-7061	20001130
US 6387944	B1	20020514	US 2000-719047	20001207
US 2002045583	A1	20020418	US 2001-773772	20010202
US 6441022	B2	20020827		
HK 1036799	A1	20040402	HK 2001-107735	20011106
PRIORITY APPLN. INFO.:			DE 1998-19825804	A 19980610
			AU 1997-23266	A3 19970311
			WO 1999-EP3701	W 19990528
			US 1999-398315	A1 19990920

OTHER SOURCE(S): MARPAT 132:35625
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. such as I (mixture of diastereoisomers) were prepared as hypolipemic agents. Thus, I was prepared in 2 sequences from racemic II and Fmoc-D-lys(Boc)-OH, followed by removal of the Fmoc group with Et2NH. I was ≥20 times more active than 3 analogous comparison substances in tests of fecal separation of 14C-taurocholic acid in rats.

IT **252372-02-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(amino acid containing benzo[b]thiepine 1,1-dioxide derivs. as hypolipemic agents)

IT **252047-42-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(amino acid containing benzo[b]thiepine 1,1-dioxide derivs. as hypolipemic agents)

IT **252372-00-2P 252372-01-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(amino acid containing benzo[b]thiepine 1,1-dioxide derivs. as hypolipemic agents)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 20 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:795802 HCAPLUS
DOCUMENT NUMBER: 132:22884
TITLE: Preparation of benzothiepine-1,1-dioxides as hypolipemics
INVENTOR(S): Frick, Wendelin; Enhsen, Alfons; Glombik, Heiner; Heuer, Hubert
PATENT ASSIGNEE(S): Hoechst Marion Roussel Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9964409	A2	19991216	WO 1999-EP3743	19990529
WO 9964409	A3	20000302		
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RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19825804	A1	19991216	DE 1998-19825804	19980610
DE 19825804	C2	20000824		
TR 200003634	T2	20010621	TR 2000-200003634	19990528
ES 2182535	T3	20030301	ES 1999-927784	19990528
PT 1086092	T	20030331	PT 1999-927784	19990528
CA 2334773	AA	19991216	CA 1999-2334773	19990529
AU 9945031	A1	19991230	AU 1999-45031	19990529
AU 752633	B2	20020926		
EP 1086113	A2	20010328	EP 1999-927802	19990529
EP 1086113	B1	20040211		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
TR 200003632	T2	20010420	TR 2000-200003632	19990529
JP 2002517490	T2	20020618	JP 2000-553418	19990529
JP 3374129	B2	20030204		
NZ 508681	A	20020628	NZ 1999-508681	19990529
RU 2220141	C2	20031227	RU 2001-101499	19990529
AT 259372	E	20040215	AT 1999-927802	19990529
US 6221897	B1	20010424	US 1999-398315	19990920
AU 761249	B2	20030529	AU 2000-53394	20000816
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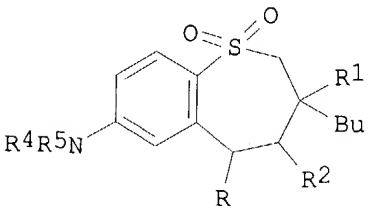
ZA 2000007061	A	20010718	ZA 2000-7061	20001130
NO 2000006251	A	20010207	NO 2000-6251	20001208
US 2002045583	A1	20020418	US 2001-773772	20010202
US 6441022	B2	20020827		
US 2003017996	A1	20030123	US 2002-201050	20020724
US 6642269	B2	20031104		
US 2004087648	A1	20040506	US 2003-606771	20030627

PRIORITY APPLN. INFO.:

DE 1998-19825804	A	19980610
US 1996-13119P	P	19960311
AU 1997-23266	A3	19970311
WO 1999-EP3743	W	19990529
US 1999-398315	A1	19990920
US 2001-773772	A1	20010202
US 2002-201050	A1	20020724

OTHER SOURCE(S): MARPAT 132:22884

GI



I

AB Title compds. [I; R = C6H4NHZR3; R1,R4,R5 = Me, Et, Pr, Bu; R2 = H, OH, amino(alkyl); R3 = sugar residue; Z = bond, carbonyl(alkylene), CONH,

etc.] were prepared Thus, I [R = C6H4(NHR')-3, R1 = Et, R2 = OH, R4 = R5 = Me](II; R' = H) was amidated by penta-O-acetyl-D-gluconic acid and the product deprotected to give II (R' = gluconoyl) as a mixture of diastereomers. Data for biol. activity of I were given.

IT **252047-36-2P 252047-37-3P 252047-38-4P**
252047-39-5P 252047-40-8P 252047-41-9P
252208-66-5P 252208-67-6P 252208-68-7P
252208-69-8P 252208-70-1P 252208-71-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzothiepine-1,1-dioxides as hypolipemics)

IT **252047-42-0 252047-43-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of benzothiepine-1,1-dioxides as hypolipemics)

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ENTER DISPLAY CODE (TI) OR ?:end

=> select hit rn l20 1-20
E491 THROUGH E563 ASSIGNED

=> fil reg
FILE 'REGISTRY' ENTERED AT 13:56:48 ON 23 OCT 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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STRUCTURE FILE UPDATES:   21 OCT 2004  HIGHEST RN 767117-28-2
DICTIONARY FILE UPDATES:  21 OCT 2004  HIGHEST RN 767117-28-2

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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=> => d his l21

     (FILE 'HCAPLUS' ENTERED AT 13:45:39 ON 23 OCT 2004)
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     FILE 'REGISTRY' ENTERED AT 13:56:48 ON 23 OCT 2004
L21           73 S E491-E563

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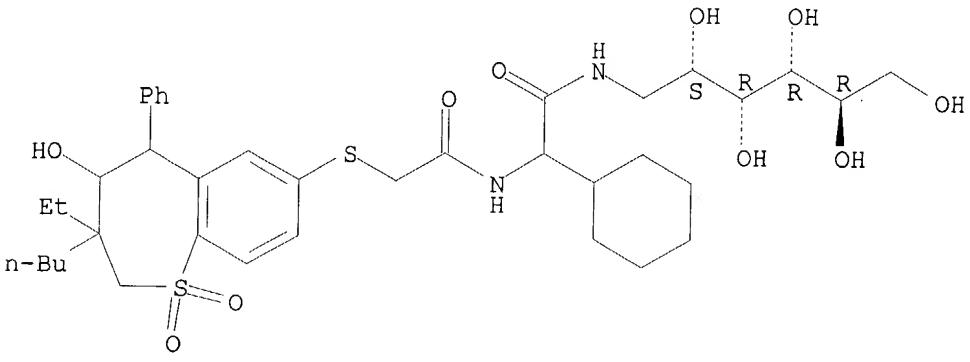
L21 ANSWER 1 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **753486-46-3** REGISTRY
CN D-Glucitol, 1-[[[[[(3-butyl-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-5-phenyl-1-benzothiepin-7-yl)thio]acetyl]amino]cyclohexylacetyl]amino]-1-deoxy- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C38 H56 N2 O10 S2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.



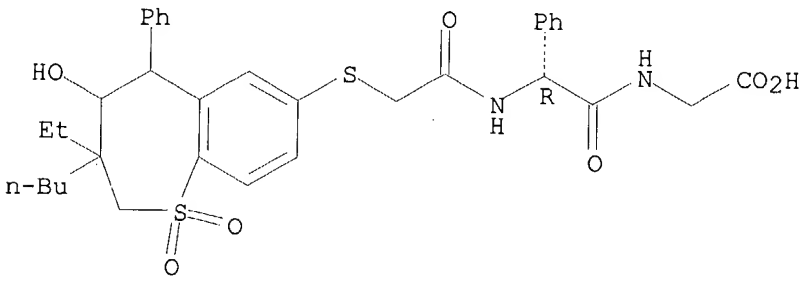
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 141:260784

L21 ANSWER 5 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **501947-90-6** REGISTRY
CN Glycine, (2R)-N-[[(3-butyl-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-5-phenyl-1-benzothiepin-7-yl)thio]acetyl]-2-phenylglycyl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C34 H40 N2 O7 S2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation)

Absolute stereochemistry.

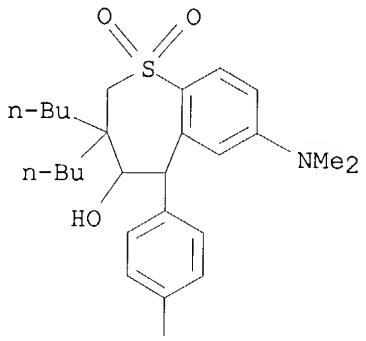


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 138:238032

L21 ANSWER 10 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **460041-94-5** REGISTRY
CN Ethanaminium, 2-[2-[2-[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]ethoxy]ethoxy]-N,N,N-triethyl-, chloride (9CI) (CA INDEX NAME)
MF C38 H63 N2 O6 S . Cl
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)
CRN (760167-75-7)



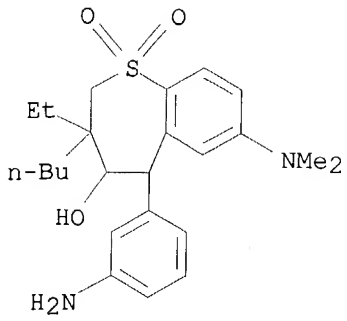
$Et_3{}^{+}N-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O$

● Cl^-

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:252985

L21 ANSWER 15 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **439114-42-8** REGISTRY
CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-, 1,1-dioxide (9CI) (CA INDEX NAME)
MF C24 H34 N2 O3 S
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: RACT (Reactant or reagent)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:63115

L21 ANSWER 20 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **439114-34-8** REGISTRY
CN Acetic acid, [2-[2-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]ethoxy]ethoxy]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
MF C30 H44 N2 O7 S . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation); RACT (Reactant or reagent)

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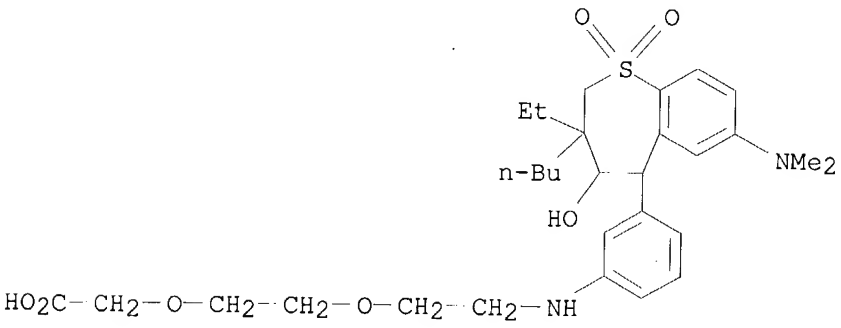
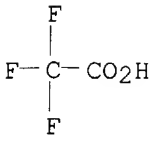
CRN 439114-33-7
CMF C30 H44 N2 O7 S



CM 2

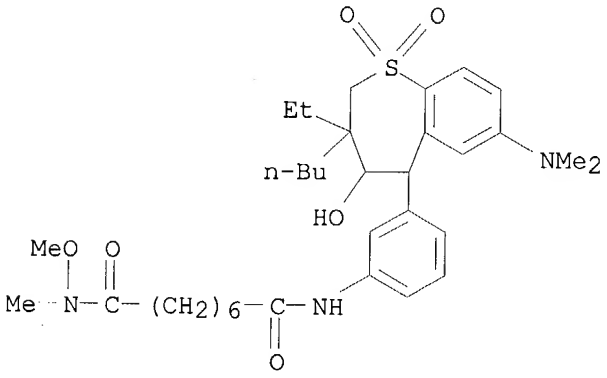
CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:63115

L21 ANSWER 25 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **439114-24-6** REGISTRY
CN Octanediamide, N'-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N-methoxy-N-methyl- (9CI) (CA INDEX NAME)
MF C34 H51 N3 O6 S
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation); RACT (Reactant or reagent)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:63115

L21 ANSWER 30 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **439114-16-6** REGISTRY
CN 4,7,10,13,16-Pentaoxanonadecanediamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N'-[[3-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
MF C63 H80 F2 N4 O12 S . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

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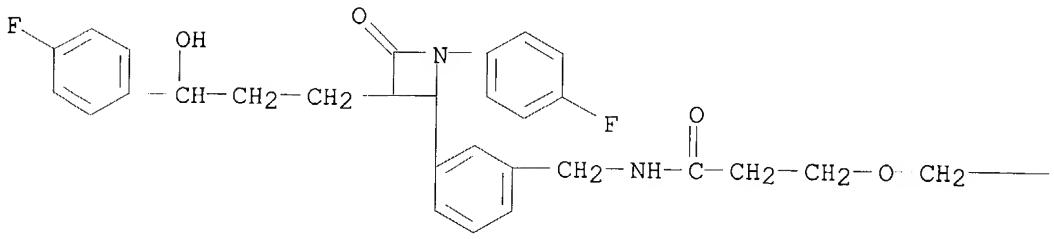
CRN 439114-15-5
CMF C63 H80 F2 N4 O12 S

PAGE 1-A



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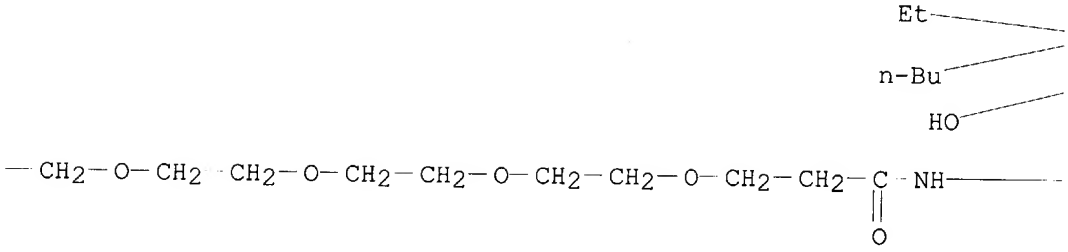

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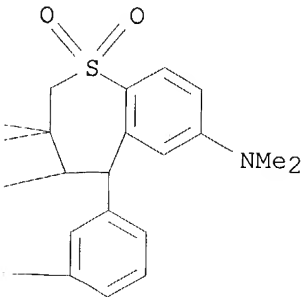

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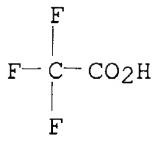


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

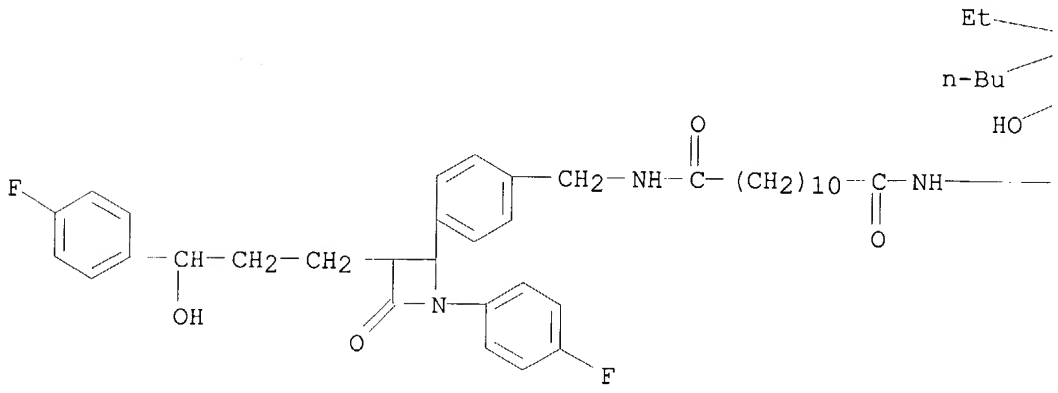
REFERENCE 1: 137:63115

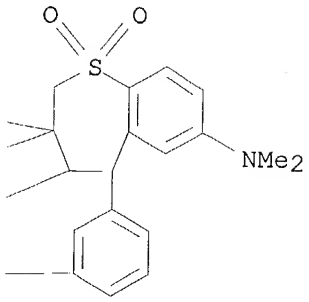
L21 ANSWER 35 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **439114-06-4** REGISTRY
CN Dodecanediamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N'-[[4-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
MF C61 H76 F2 N4 O7 S . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

CM 1

CRN 439114-05-3
CMF C61 H76 F2 N4 O7 S

PAGE 1-A





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CRN 76-05-1
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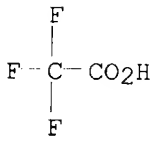


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

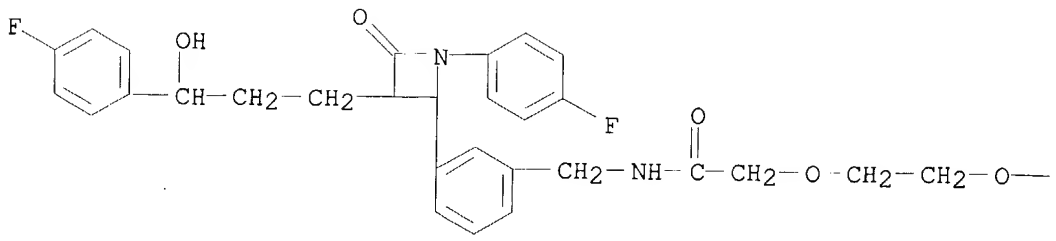
REFERENCE 1: 137:63115

L21 ANSWER 40 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **439113-98-1** REGISTRY
CN Acetamide, 2-[2-[2-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-2-oxoethoxy]ethoxy]-N-[[3-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
MF C55 H64 F2 N4 O9 S . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

CM 1

CRN 439113-97-0
CMF C55 H64 F2 N4 O9 S

PAGE 1-A



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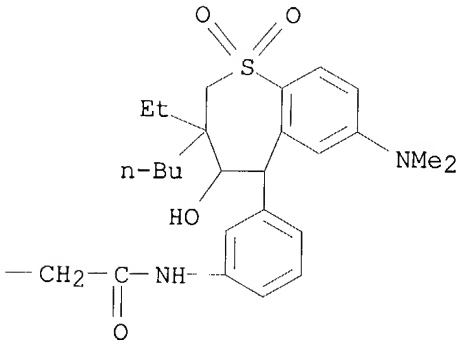
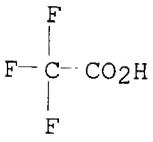


CM 2

CRN 76-05-1
CMF C2 H F3 O2



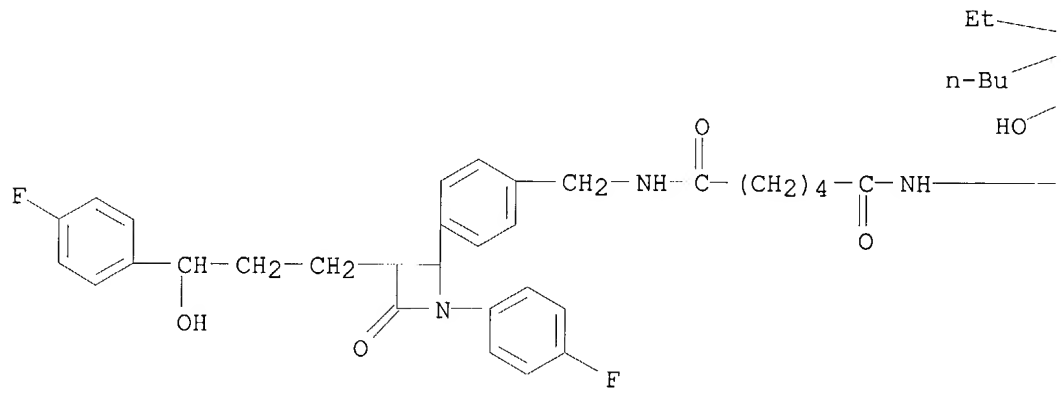
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:63115

L21 ANSWER 45 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **439113-91-4** REGISTRY
CN Hexanediamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N'-[[4-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)
MF C55 H64 F2 N4 O7 S
SR CA

LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

PAGE 1-A



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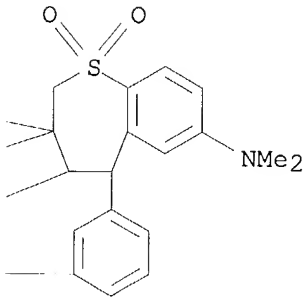


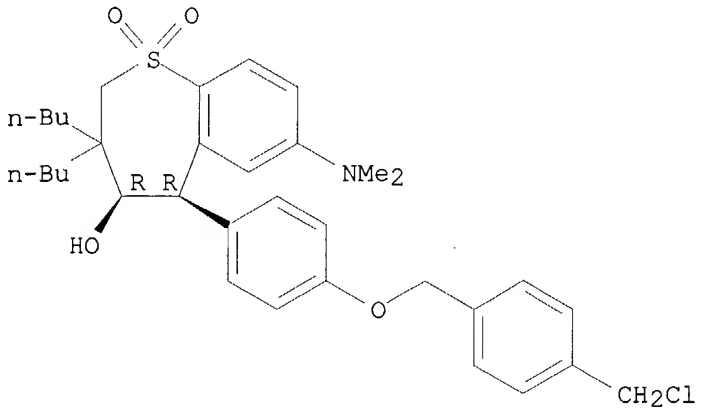
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:63115

L21 ANSWER 50 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **289038-78-4** REGISTRY
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-5-[4-[[4-(chloromethyl)phenyl]methoxy]phenyl]-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C34 H44 Cl N O4 S
SR CA
LC STN Files: CA, CAPLUS, USPAT2, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation); RACT (Reactant or reagent)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

6 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:111291

REFERENCE 2: 139:323443

REFERENCE 3: 138:385315

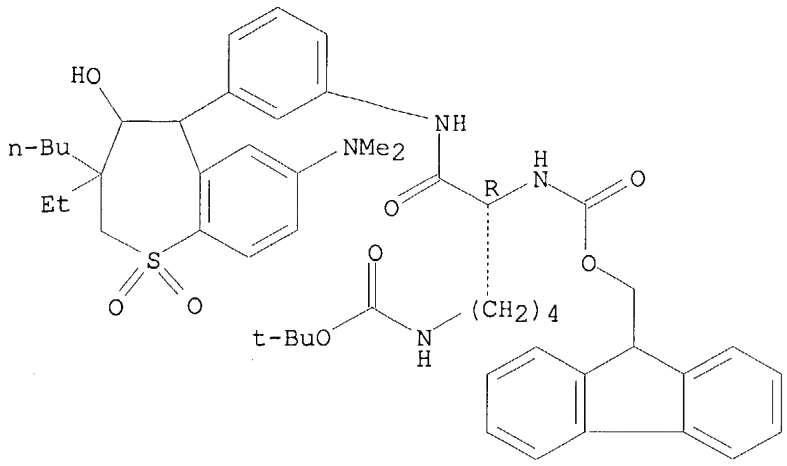
REFERENCE 4: 135:257255

REFERENCE 5: 135:257253

REFERENCE 6: 133:193089

L21 ANSWER 55 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **252372-00-2** REGISTRY
CN Carbamic acid, [(1R)-1-[[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]carbonyl]-5-[[(1,1-dimethylethoxy)carbonyl]amino]pentyl]-, 9H-fluoren-9-ylmethyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C50 H64 N4 O8 S
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation); RACT (Reactant or reagent)

Absolute stereochemistry.



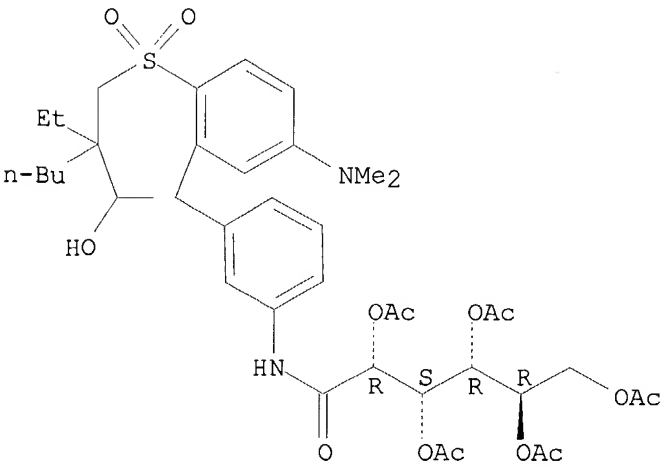
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 132:35625

L21 ANSWER 60 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **252208-67-6** REGISTRY
CN D-Gluconamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, 2,3,4,5,6-pentaacetate (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C40 H54 N2 O14 S
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.



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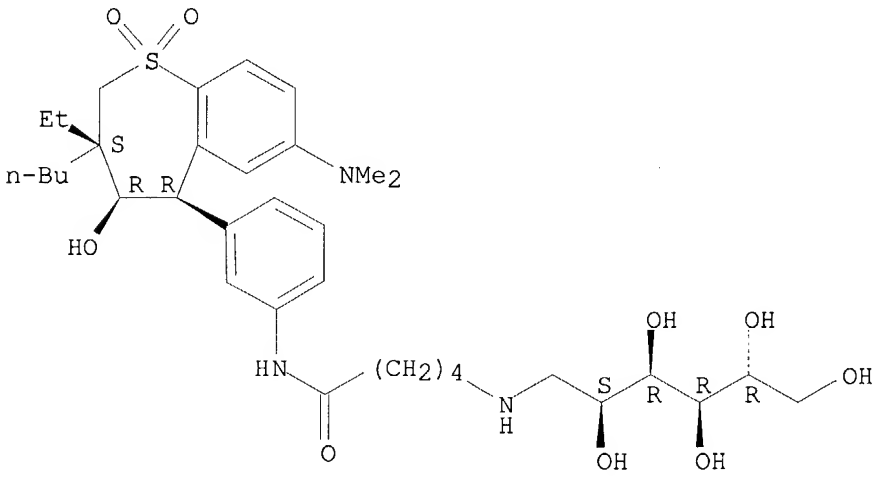
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 132:22884

L21 ANSWER 65 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **252047-40-8** REGISTRY
CN D-Glucitol, 1-[[5-[[3-[(3S,4R,5R)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]amino]-1-deoxy- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C35 H55 N3 O9 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.



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3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 141:17641

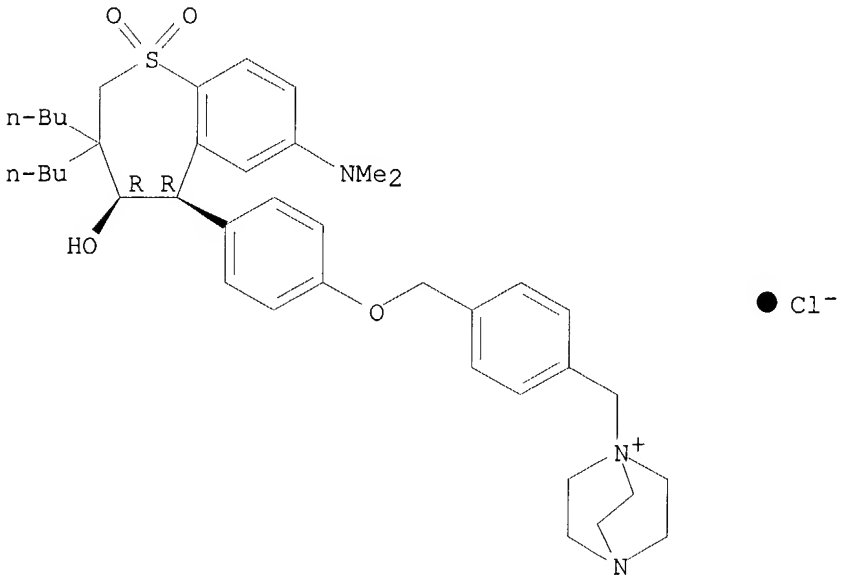
REFERENCE 2: 138:215326

REFERENCE 3: 132:22884

L21 ANSWER 70 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **228113-66-4** REGISTRY
CN 4-Aza-1-azoniabicyclo[2.2.2]octane, 1-[[4-[[4-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-, chloride (9CI) (CA INDEX NAME)
FS STEREOSEARCH

MF C40 H56 N3 O4 S . Cl
SR CA
LC STN Files: CA, CAPLUS, CASREACT, USPAT2, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study)
CRN (716313-53-0)

Absolute stereochemistry.



8 REFERENCES IN FILE CA (1907 TO DATE)
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REFERENCE 1: 140:350330

REFERENCE 2: 140:111291

REFERENCE 3: 139:323443

REFERENCE 4: 138:385315

REFERENCE 5: 135:257255

REFERENCE 6: 135:257253

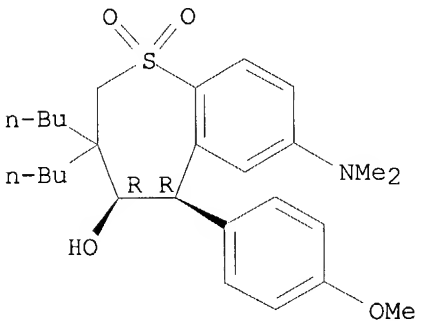
REFERENCE 7: 133:193089

REFERENCE 8: 131:58769

L21 ANSWER 73 OF 73 REGISTRY COPYRIGHT 2004 ACS on STN
RN **197373-42-5** REGISTRY
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-, 1,1-dioxide, cis-
OTHER NAMES:

CN cis-3,3-Dibutyl-7-(dimethylamino)-1,1-dioxido-4-hydroxy-5-(4-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine
FS STEREOSEARCH
MF C27 H39 N O4 S
SR CA
LC STN Files: CA, CAPLUS, CASREACT, USPAT2, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

14 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
14 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:111291

REFERENCE 2: 139:323443

REFERENCE 3: 138:385315

REFERENCE 4: 135:257255

REFERENCE 5: 135:257253

REFERENCE 6: 135:137410

REFERENCE 7: 133:193089

REFERENCE 8: 133:94516

REFERENCE 9: 133:94515

REFERENCE 10: 133:84286

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